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NARRATIVE REVIEW

Does it matter if I am overweight? 3. Important co-morbidities of obesity.

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Abstract

Objective: The objective of this narrative review is to consider the impact of various levels of obesity upon the risks of premature mortality, a reduced-quality-adjusted life span, and various clinically important co-morbidities. ***Methods.*** Information obtained from Ovid/Medline and Google Scholar through to November 2018 was supplemented by a search of the author's extensive personal files. ***Results.*** Overweight has only a limited adverse effect upon these several risks, but dangers increase steeply with further fat accumulation; thus severe (type III) obesity greatly augments the risk of premature death, shortening a person's average lifespan by several years. In addition, the obese individual faces a substantial loss of quality-adjusted life years due to effects from various co-morbidities, including (in order of importance to health expectancy) problems arising from the heart and circulation, neoplasms, diabetes mellitus, vascular diseases of the brain, pneumonia and influenza, digestive and renal diseases, accidents and homicides. Various potential covariates of obesity have been considered in epidemiological analyses, but if habitual physical activity has been considered at all, it has typically been represented by a weak questionnaire assessment. Nevertheless, evidence is emerging that obesity and an inadequate level of habitual physical activity have at least partially independent adverse effects upon both life expectancy and quality-adjusted life span. ***Conclusions.*** Severe obesity has a substantial negative effect upon both life expectancy and quality-adjusted life span, thus providing yet one more good reason for health practitioners to advocate maintenance of an ideal body mass. **Health & Fitness Journal of Canada 2018;11(4):3-65.**

Keywords: Cancer; Cardiovascular disease; Diabetes mellitus; Healthy life years; Life expectancy; Metabolic syndrome; Neoplasia; Preventive medicine.

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Introduction

The two previous articles in this trilogy have examined the impact of obesity upon an individual's biomechanics, physiology and physical performance (Shephard, 2018a), and the negative psycho-social consequences of an excessive body mass (Shephard, 2018c). In the final segment of this extended review, we turn to the more widely recognized and discussed issues of the multiple co-morbidities that are associated with an accumulation of body fat, and their respective impacts upon life expectancy and quality-adjusted life-years.

Many authors have simply assumed that there is a direct causal relationship between the accumulation of an excessive amount of body fat and various chronic diseases. However, there is a need to look carefully at two alternative hypotheses. Firstly, an inadequate level of habitual physical activity may have precipitated the morbid condition under consideration (for example, ischaemic heart disease), and a well-recognized by-product of an inadequate level of daily exercise is an excessive accumulation of body fat. Secondly, symptoms associated with the morbid condition (for example, osteo-arthritis) may have seriously restricted the physical activity of an individual, and

this in turn is likely to have led to an accumulation of body fat. There are several practical difficulties in disentangling the respective effects of obesity, physical inactivity and chronic disease. Many of the available studies are cross-sectional in type, rather than prospective or experimental in design. Moreover, whereas most reports are based on a fairly reliable approximation of body fat content (commonly using the BMI rather than more objective measurements such as determinations of body fat content), any determinations of habitual physical activity have usually been limited to a rather weak and inaccurate 3-4 level questionnaire classification of activity patterns.

For the past several decades, most western nations have faced the consequences of an "obesity epidemic" (Shephard, 2018a). Insurance agencies have long recognized that an accumulation of excessive body fat, as signaled by an "undesirable weight", is associated with poor survival prospects (Metropolitan Life Insurance, 1983; Shephard, 2018d; Society of Actuaries, 1959), and clients' departures from "ideal" body mass values have been factored into their calculation of life insurance premiums. In this review, we will examine closely the costs of the epidemic, in terms of a reduced life expectancy, and thus a shortening of average life span. We will also look at the impact of the growing prevalence of obesity upon co-morbidities and the quality of life. The World Health Organization asserted that over the past 30 years, increases in the prevalence of obesity were accompanied by a dramatic rise in the incidence of type 2 diabetes mellitus (World Health Organisation, 2002). Indeed, in one U.S. study, 53% of all deaths in women with a BMI >29 kg/m^2 were attributed to some co-morbidity of obesity (Manson et al.,1995). The long litany of chronic diseases that are associated with an excessive accumulation of body fat now accounts for a substantial fraction of all health-care costs in many industrialized countries (Shephard, 2019).

The obesity-associated risk of mental disorders (anxiety, depression and suicide) has been discussed in a previous section of this review (Shephard, 2019). In this article, we will look at the high overall mortality, and the increased risk of a multitude of other clinically significant co-morbidities faced by those who are obese (Table 1). In many but not all of the conditions listed, the co-morbidity seems particularly likely to develop if the accumulated fat shows a central, android distribution (Shephard, 2017).

Overall premature mortality and loss of quality-adjusted life-years

General considerations. The age at which a person's death may be considered as premature is a personal decision, but there is certainly a fair consensus that most people would wish to live at least until their normal age of retirement (perhaps at an age of 65 years), and most would probably like to live in good health for a few subsequent years, when their accumulated dreams and ambitions can be pursued.

Table 1: Co-morbidities associated with an excessive accumulation of body fat.

- High overall premature mortality, with additional loss of quality-adjusted life years
- Cardiovascular disease (hypertension, atherosclerosis and stroke)
- Neoplasms (breast, prostate, colon, endometrial, kidney, gallbladder, and liver)
- Type 2 diabetes mellitus and metabolic syndrome
- Abdominal conditions (non-alcoholic fatty liver disease, acute pancreatic disease, gall bladder disease)
- Chronic renal disease
- Respiratory conditions (asthma, influenza, pneumonia)
- Osteoarthritis and chronic back pain
- Increased risk of abdominal surgery and greater likelihood of post-operative complications
- Accidents, suicides and mental illnesses

The mortality tables of the Society of Actuaries have long recognized as providing a simple measure of the impact of an excess of body fat upon the risk of premature mortality (Metropolitan Life Insurance, 1983; Shephard, 2018d; Society of Actuaries, 1979), and indeed the companies concerned have adjusted the premiums charged to individual clients based upon such data.

Andres et al. (1985) noted that in terms of mortality experience, there was a U-shaped relationship between body mass and the average age at death. There was some increase of mortality in individuals with a very low body weight (partly reflecting smokers and individuals already affected by chronic disease), and a much larger disadvantage of life expectancy among those who were grossly obese. Perhaps equally importantly (but not considered in the actuarial data), an obese person faced the additional penalty of a substantial range of co-morbidities that shortened their quality-adjusted life span.

One analysis of data from the NHANES study showed that for a 20-year old adult, the average remaining years of life were shortened by 9-13 years in those with a BMI > 35 kg/m^2 (Fontaine et al., 2003), a lifespan loss of around 10%. If data are followed longitudinally, there seems a lag-time of 10 or more years between the onset of obesity and the appearance of many of its adverse effects upon mortality statistics (Simopoulos and Van Itallie, 1984; Arnlov et al., 2010). The full adverse impact of fat accumulation upon health may thus be missed unless there is a long-term follow-up of study participants.

Importantly from the viewpoint of prevention, substantial reductions in subsequent mortality have been seen in morbidly obese individuals who have succeeded in reducing their weight following gastric by-pass surgery (Adams et al., 2007; Sjöström et al., 2007).

Limitations of data. Care must be shown in interpreting the insurance mortality data because of several fundamental limitations inherent in these numbers. Data were based on the height and weight of the individual when life insurance was purchased, and this often was as a young adult, before the onset of obesity. Moreover, figures were necessarily based on that upper socio-economic segment of the population who were interested in and able to buy life insurance. Further, the basic data for height and body mass were either self-reported (leading to an over-estimation of height and an under-estimation of body mass), or were collected by medical office staff, with the applicants wearing shoes and indoor

clothing (in some cases, crude corrections were then applied for these sources of error). Finally, many of the early data sets, including those of the actuaries, took no account of the individual's habitual physical activity or smoking habits, both of which have strong interactions with obesity as long-term determinants of life expectancy (Ekelund et al., 2015).

Data from some 23 populations world-wide have pointed to rather similar average nadirs of the BMI/life-expectancy curve, in the BMI range 20-25 kg/m^2 (Andres et al., 1985). After making arbitrary corrections for clients' shoe heights and the weight of their clothing, nadirs derived from the Actuarial data have varied from 21.4 kg/m^2 in men and 19.5 kg/m^2 in women in the youngest age group (20-29 yr) to 26.6 and 27.3 kg/m^2 in those aged 60-69 years (Table 2). An age-related increase in nadirs of at least 2 kg/m^2 has been observed consistently in the oldest subject-groups (Allison et al., 1997; Childers and Allison, 2010; Matsuo, et al., 2008; Sorkin, 2014; Winter et al., 2014). Moreover, the average nadir seems to be lower for women than for men, at least in the youngest age group.

These differences can be understood in terms of the limitations of BMI as a measure of body fat content. Unfortunately, it is far from being a perfect measure of fat accumulation- it is also modified by muscle development or wasting, and by the presence of dense or osteoporotic bones. Moreover, the BMI does not distinguish between overall body fat content and the proportion of abdominal fat (although the latter may be the more important determinant of premature mortality). Further, smoking increases mortality and tends to be associated with a low BMI (Allison et al., 1997; Simopoulos and Van Itallie, 1984), and BMI is also reduced by general frailty

Table 2: Nadirs of the BMI/life expectancy curves (kg/m^2), as seen in insurance data (Society of Actuaries, 1959), after making arbitrary crude corrections for shoe height and the weight of indoor clothing (based on data of Andres et al., 1985).

Age group	Men	Women
20-29 yr	21.4	19.5
30-39 yr	21.6	23.4
40-49 yr	22.9	23.2
50-59 yr	25.8	25.2
60-69 yr	26.6	27.3

and the chronic disease of old age. Finally, there are problems in interpreting the BMI because of the age-related decrease of stature Nevertheless, the general shape of the BMI/mortality curve certainly points to an adverse effect of fat accumulation upon life expectancy. Andres et al. (1985) did not report on habitual physical activity levels in their sample, but it seems likely that the rightward displacement of the nadir of the BMI/age curve, as seen in the 2 oldest age categories reflects in part the greater preservation of lean tissue and bone mass, and associated health benefits, in the most active members of their subject group.

Impact of obesity on the odds of premature death. A European prospective study followed 359,387 adults initially aged 51.5 years for an average of 9.7 years, looking at the health impacts of a combination of BMI, waist circumference and waist-hip ratio (Pischon et al., 2008). After adjusting data for education, smoking, alcohol consumption and habitual physical activity (a crude, 4-level classification), the odds ratios of death over a 9.7-year follow-up for those having waist circumferences in the highest quintile

were 2.05 and 1.78, and the corresponding figures for those having the highest quintile of waist-hip ratio were 1.68 and 1.51. Interestingly, BMI remained a statistically significant risk factor for premature death, even in models that included waist circumference or waist-hip ratio. Nevertheless, this does not establish that BMI is the primary cause of an adverse prognosis; it may simply be co-varying with other unmeasured risk factors such as an inadequate level of habitual physical activity, a poor diet, or a genetic predisposition to premature death (Hernán and Taubman, 2008). As noted above, many of the early studies also did not exclude smokers, or those with pre-existing disease, but this is an important precaution when assessing the impact of obesity, since both of these factors modify the shape of the BMI/mortality curve (Patel, Hildebrand, and Gapstur, 2014). Both smoking and low oestrogen levels led to increases of mortality among very lean women in the Seventh-Day Adventist sample (Singh, Linsted, and Fraser, 1999).

The influence of the length of follow-up was also examined in a 26-year study on non-smoking 7th-Day Adventist women. Obesity had an adverse effect, whether the follow-up was for 8, 14 or 26 years (Table 3), but if this study had been terminated at 8 years, it seems the effect of obesity would have been under-estimated.

Calle et al. (1999) collected prospective data on a sample of over 1 million U.S. adults who were followed for 14 years. This data set is interesting in that data were said to have been adjusted for habitual physical activity (although the method of determining activity patterns was not specified). The risk of death was greater in smokers or former smokers than in nonsmokers, and was also greater in those with any type of pre-existing disease. Moreover, the risk of death at any given body mass was found to be greater in "white" than in "black" individuals. At all ages, the impact of gross obesity upon non-smokers, free of disease, was substantial (Table 4). However, as in earlier analyses, the adverse effect of excess weight was smaller in the oldest age category.

A similar, 10-yr, prospective study examined 16,087 deaths in 1.46 million "white" adults (de Gonzalez, Hartge, and Cerhan, 2010) who were healthy non-smokers with an initial average age of 58 years.. After adjusting for alcohol use, marital status, education and "overall physical activity," the odds of dying for women with a self-reported BMI of 30-34.9 kg/m^2 was 1.44, for a BMI of 35.0-

Table 3: Influence of length of follow-up on impact of obesity upon mortality risk as seen in non-smoking Seventh-Day Adventist women (hazard ratios based on data of Linsted and Singh, 1979, relative to quintile I of their sample, BMI < 21.3 kg/m^2).

Initial subject age and length of follow-up	BMI 23.0-24.9 kg/^{2}	BMI 24.9-27.4 kg/m^2	BMI >27.4 kg/m^2
8 years			
30-54 yr	0.56	0.87	1.14
55-74 yr	0.50	0.66	1.07
14 years			
30-54 yr	0.86	1.23	1.81
55-74 yr	0.84	1.02	1.34
26 years			
30-54 yr	0.87	0.98	1.64
55-74 yr	1.13	1.12	1.29

39.9 kg/m^2 it was 1.88, and or a BMI >4 kg/m^2 it was 2.51, with rather similar odds in the men.

Many investigators have suggested the relationship is J- rather than U-shaped (Table 4); there is little or no increase of mortality until a BMI >27.5 kg/m^2 is passed (Sorkin, Miller, and Andres, 1994), but a steep increase of premature mortality is seen among those with type II and type III obesity.

The Global BMI Mortality Collaboration (2016) amassed data from 3,951,455 participants in 189 studies of non-smokers without pre-existing disease who had been followed for the rather short average time of 5 years.

Hazard ratios relative to those with a normal body mass (unadjusted for habitual physical activity or covariates other than age and sex) were for the three grades of obesity 1.45, 1.94 and 2.76. A further investigation (Flegal et al., 2013) collected and analyzed data from 97 prospective trials; this analysis apparently did not adjust for covariates, nor did it eliminate smokers or those with pre-existing disease; perhaps for this reason, it found somewhat smaller effects (hazard ratios of 0.95 for grade I, and 1.29 for grades 2 and 3 obesity).

Decrease in life-expectancy. Many clients of health practitioners have difficulty in understanding and weighing concepts such as the adverse odds ratio or hazard ratio that is associated with obesity; however, the dangers become much more comprehensible and of practical value to front-line workers if they are translated into an equivalent potential shortening of life expectancy (Robertson et al., 2013).

Estimates of the number of years lost are generally made mathematically by an arbitrary and somewhat imprecise tactic: integrating over a person's average remaining life span the year-by-year losses of life expectancy calculated as the risk of death for a given year in a person of normal weight, multiplied by the odds or hazard ratio of increased mortality in an obese individual during that same year of life. The losses calculated in this fashion can be quite dramatic. For instance, Chang and colleagues (2013) estimated that the reduction of life expectancy could be as much as 11.7 years in obese "black" males, and 7.5 years in those of normal weight.

In general, analyses have taken no account of the likely effect of substantial and obesity-linked inter-individual differences in habitual physical activity. Finkelstein et al. (2003) exploited findings from the NHANES II Study, which measured BMI values during the 1970s, and examined mortality experience

Table 4: Multivariate-adjusted odds ratio of death of healthy non-smokers from all causes over a 14-year prospective trial. Findings shown as hazard ratios relative to individuals with a BMI of 23.5-24.9 kg/m^2, adjusted for age, education, physical activity, alcohol use, fat consumption, vegetable consumption and oestrogen replacement therapy. Based on data of Calle et al., (1999).

Sex and age group	BMI 23.5-24.9 kg/m^2	BMI 28.0-29.9 kg/m^2	BMI 30.0-31.9 kg/m^2	BMI 32.0-34.9 kg/m^2	BMI >35 kg/m^2
Men					
30-64 yr	1.00	1.41	1.62	2.05	2.30
65-74 yr	1.00	1.34	1.42	1.85	2.75
>75 yr	1.00	1.21	1.16	1.31	1.53
Women					
30-64 yr	1.00	1.33	1.51	1.53	1.86
65-74 yr	1.00	1.28	1.32	1.71	1.99
>75 yr	1.00	1.15	1.25	1.36	1.53

through to 1992. They obtained estimates of years lost by obese individuals at all initial ages from 18 to 45 years, and in those who were initially aged 40 they set the adverse effects of a BMI >38 kg/m^2 at a 4-year loss of life in "white" men, and a 3-year loss in "white" women, with smaller effects in "blacks;" the ethnic differences may reflect differing competing risks such as homicide, racial differences in smoking and physical activity habits, and/or differing distributions of body fat in the two racial groups. Finkelstein et al. (2003) went on to analyze data by age (18 vs. 40 vs. 65 years), race and smoking habits, and argued that adverse effects were only seen with severe obesity; thus, taking data at age 40 years for white subjects, the respective shortenings of lifespan were 1, 5 and 9 years for the three grades of obesity in non-smoking men, and 1, 4 and 7 years in non-smoking women. Finkelstein et al. (2010) examined data from the U.S. National Health Interview Survey. Again, they found relatively little effect from being overweight or mildly obese, but a substantial number of anticipated life-years were lost in those with marked obesity.

The findings from other available surveys are somewhat variable, but in general support this conclusion (Table 5); several large studies show substantial adverse effects upon the life expectancy of the obese and grossly obese. Stevens et al. (1999) looked at data for the 62,116 male and 262,965 female non-smoking "white" adults who were enrolled on the U.S. Cancer Prevention Study; the average loss in the obese (BMI > 30 kg/m^2) was less than one calendar year, but the impact of fat accumulation was larger among older participants in this study (Table 6), The authors of this report admitted that estimates lacked accuracy in the youngest age groups, due to a follow-up of only 11 years. But possibly, the observed age trend reflects an increasing influence of low levels of habitual physical activity upon survival in older obese adults. Muening et al. (2006) drew their data from 13,646 participants in the U.S. National Health Interview Survey of 1990-1992. Like Stevens et al. (1999), they highlighted an increased adverse impact of obesity in the older age groups. Smoking habits were not analyzed in this study, but a BMI > 30 kg/m^2 was shown to have substantial adverse effects upon life expectancy, even at the age of 18 years. For those aged 20-39 years, the years of calendar life lost by the obese were 8.2 in men and 5.0 in women. However, at age 40-59 years, losses had decreased to 3.8 and 4.1 years, and in those aged 60-79 years they were only 0.7 and 1.8 years. Grover et al. (2015) also looked at the effects of age; in contrast to the other two reports, the adverse effects of obesity seemed to diminish with age in their data.

Peeters et al. (2003) examined a relatively small sample of participants in the Framingham study, initially aged 30-49 years. After separating data for smokers and non-smokers, losses of life-years in both categories were quite large for those with a BMI >30 kg/m^2. Reuser et al. (2008) obtained data on older individuals (55-80 years, and > 80 years), and they concluded that in these age categories fat accumulation did not have any substantial adverse effect unless the obesity was gross (BMI >35 kg/m^2); then, losses in life expectancy of 3.0 and 5.2 years were seen in men and women, respectively.

Table 5: Calendar years of subsequent expected life lost by adults who are overweight or obese at specified ages in their life course.

Authors	Initial age	Males		Females	
		Overweight	Obese	Overweight	Obese
Muening et al. (2006)	18 yr	0.3 yr	2.7 yr	1.1 yr	2.8 yr
Stevens et al. (1999)	40-49 yr	0.1 yr	0.7 yr	0.1 yr	0.4 yr
Peeters et al. (2003)	40 yr (non-smokers)	3.1 yr	5.8 yr	3.3 yr	7.1 yr
Peeters et al. (2003)	40 yr (smokers)	1.3 yr	6.7 yr	0.2 yr	7.2 yr
Finkelstein et al. (2010)	40 yr (white non-smokers)	0 yr	5 yr Class II 9 yr Class III	0 yr	4 yr Class II 7 yr Class III
Fontaine et al. (2003)	40 yr ("white")	0 yr (BMI = 27 kg/m^2)	4 yr (BMI = 38 kg/m^2)	0 yr (BMI = 27 kg/m^2)	3 yr BMI = 38 kg/m^2)
Fontaine et al. (2003)	40 yr ("black")	0 yr (BMI = 27 kg/m^2)	3 yr (BMI = 38 kg/m^2)	-1 yr (BMI = 27 kg/m^2)	0 yr (BMI = 38 kg/m^2)
Moore et al. (2008)	40 yr			1.8 yr (BMI 25-30 kg/m^2)	5.0 yr (BMI >30 kg /m^2)
Grover et al. (2015)	40-59 yr	1.1 yr	3.8 yr	1.8 yr	4.1 yr
Ashwell et al. (2014)	50 yr	0.55 yr (BMI) 0.7 yr (W/H)	4.7 yr (BMI = 35 kg/m^2) 5.8 (W/H)	0.55 yr (BMI) 0.7 (W/H)	2.1 (BMI = 35 kg/m^2) 4.1 (W/H)
Reuser et al. (2008)	55-80 yr	-0.6 yr	3 yr (severely obese)	-0.7	5.2 yr (severely obese)

Moore et al. (2008) analyzed findings for 50,186 women. This study measured initial heights and weights, and importantly it also obtained data on habitual physical activity (the daily amount of time spent on moderate and vigorous physical activity during the preceding year); the resulting physical activity index was inversely related to the Individual's BMI, and data were adjusted for physical activity quintiles. They noted deaths over the first 10 years of observation, and found that the adverse influence of BMI upon life expectancy persisted after adjustments for habitual physical activity.

Ashwell et al. (2014) compared estimates of years of life lost in terms of BMI and waist/height ratios, concluding (on the basis of a steeper age-related

Table 6: Influence of sex and age on years of years of anticipated lifespan lost by overweight (BMI 25-30 kg/m^2) and obese individuals i(BMI > 30 kg/m^2)(based on data of Stevens et al., 1999).

Age group (yr)	Men		Women	
	Overweight	Obese	Overweight	Obese
30-39	0.53	1.06	0.54	0.91
40-49	0.95	1.56	0.79	1.12
50-59	1.70	2.24	1.19	1.68
60-69	2.61	3.08	1.91	2.46
70-79	3.30	3.71	2.50	3.00

Table 7: Decrease of life expectancy and additional losses of health-related quality-adjusted life expectancy (years) attributable to obesity at the age of 18 years (based on data of Muening et al., 2006).

	Men			Women		
BMI (kg/m²)	23-25	25-30	>30	23-25	25-30	>30
Life expectancy	57.0	56.7	54.3	63.5	62.4	60.7
Loss of life expectancy		0.3	2.7		1.2	2.8
Quality-adjusted life expectancy	50.5	50	46.1	55.6	52.7	48.4
Added loss		0.5	4.4		3.9	7.2

increase in mortality) that the latter provided a better estimate of years lost. It thus seems that the larger body of BMI-related data provides a minimum estimate of the adverse effects of obesity upon life expectancy.

Decrease in healthy life-years. From a policy point of view, it is important to consider not only calendar years of survival, but also the quality of life that the individual enjoys. Many investigators have looked at the health-related quality of life, using the SF-36 questionnaire (a short-form survey developed by the Rand Corporation, which evaluates 4 physical and 4 mental scales of health). But arguably, in terms of obesity, the critical factor is a Gestalt of the limitations in physical and mental health, together with the adverse impact of the psycho-social constraints faced by the obese individual (Shephard, 2018c).

The impact of obesity upon quality-adjusted life expectancy may be as great or even greater than the effect upon absolute life span (Backholer et al., 2012; Reynolds et al., 2005; Walter et al., 2009). Thus, Grover et al. (2015) estimated that at any given age, the healthy life years lost to obesity were 2-4 times greater than the absolute loss of life. It is useful to estimate the total loss of quality-adjusted life expectancy, and to examine the influence upon this figure of each of the various co-morbidities of obesity.

The magnitude of the additional losses due to a reduced health-related quality of life can be seen in the calculations of Muening et al. (2006) (Table 7) and of Grover et al. (2015), (Table 8). The impact

Table 8: Influence of a person's age upon the obesity-related loss of actual (A) and healthy life (QA) years based on data of Grover et al., 2015.

	Men			Women		
	20-39 yr	**50-59 yr**	**60-79 yr**	**20-39 yr**	**50-59 yr**	**60-79 yr**
			Overweight			
A	4.5 yr	1.1 yr	0.1 yr	2.6 yr	1.8 yr	0.8 yr
QA	7.5 yr	2.5 yr	0.5 yr	6.5 yr	4.4 yr	3.7 yr
			Obese			
A	8.2 yr	3.8 yr	0.7 yr	5.0 yr	4.1 yr	1.8 yr
QA	13.6 yr	7.2 yr	2.5 yr	14.6 yr	12.4 yr	6.9 yr
			Grossly obese			
A	11.9 yr	5.2 yr	1.5 yr	6.3 yr	6.1 yr	1.3 yr
QA	21.9 yr	12.5 yr	4.1 yr	21.3 yr	17.6 yr	8.1 yr

of obesity upon both total and healthy life years seems to be much greater for the young than for elderly individuals (Table 8). Notice also that losses of health-related quality of life or healthy life years are compounded by the psycho-social pressures of obesity, as discussed in the earlier part of this trilogy (Shephard, 2018c). Jia et al. (2010) further pointed to the increasing prevalence of obesity, and estimated that because of this trend, the average loss of quality-adjusted life years in the U.S. had increased by 127% between 1993 and 2008. Information regarding the impact of obesity in children is less plentiful, but available observations point to a reduction in the health-related quality of life from quite a young age (Wille et al., 2008).

Increased risk of chronic diseases associated with obesity.

Cunningham et al. (2011) noted that the diabetes-free life expectancy of 18-year-old U.S. adults decreased by an average of 1.7 years for men and 1.5 years for women between the 1980s and the 2000s, this change being due almost entirely to a greater prevalence of obesity in the American population. The risk of developing each of the various co-morbidities associated with obesity (Table 1) has indeed increased in step with indicators of a growing average body fat content, such as the body mass index.

Since most of the conditions under consideration have multiple aetiologies, any assessment of their impact upon the overall health and mortality of a given community, requires the calculation of population attributable risks. These are determined from the prevalence of a given disorder, its impact upon health or mortality, and the fraction of that adverse impact which is due to obesity. Some of the relevant data was collected by the Society of Actuaries (1959). They related the increased risk of premature death that was associated with various pathologies to increments of body mass above "Ideal" values for height (Table 9). However, their list presents odds ratios, rather than

Table 9: Mortality of grossly obese men and women from various chronic diseases, expressed as a percentage of mortality anticipated for those of "Ideal" body mass. Based on data of the Society of Actuaries (1959).

Clinical condition	Men			Women		
	A*	B*	C*	A*	B*	C*
Diabetes mellitus	178	385	629	270	242	350
Digestive diseases	147	197	298	140	200	225
Renal diseases	141	230	298	93	122	-
Vascular diseases of brain	136	163	215	143	145	210
Heart and circulation	131	155	185	175	178	217
Pneumonia and influenza	128	103	242	148	110	-
Accidents and homicides	109	126	120	85	98	-
Suicides	71	104	142	47	-	-
All conditions	121	145	168	130	138	178

*Obesity expressed as kilograms of excess body mass relative to stature, for men and women
A = ~24 to ~28 kg; B = ~33 to ~37 kg, C = ~42 to ~46 kg.

showing the importance of individual conditions in terms of increments in the total number of premature deaths. Moreover, the mortality associated with a number of these disorders has probably changed since 1959 (for example, the availability of antibiotics and flu vaccines has dramatically reduced the number of deaths attributable to pneumonia and influenza). Further, the table makes no allowance for the possible contribution of inter-individual differences in habitual physical activity to the apparent adverse effect of obesity. However, taking the list at its face value, the dominant obesity-related increment in the risk of premature death in both sexes is associated with type 2 diabetes mellitus. Other important increases of risk are associated with heart disease and (in women) chronic renal disease.

A more recent meta-analysis of 20 individual prospective studies (Kitahara et al., 2014) placed heart disease, cancer and diabetes mellitus as the primary causes of both the increase in risk and the total number of deaths seen over an average follow-up of 10 years, at least with respect to the grossly obese (Table 10). Each of the included studies was based upon non-smokers, and comprised a total of more than 1000 deaths over at least 5 years of follow-up. The total numbers of grossly obese individuals were 1575 men and 7989 women. Overall age-adjusted death rates per 100,000 individuals per year were 347 and 284 in men and women with a normal body mass, compared with 866 and 663 in those with Class III obesity.

We will now consider the impact of obesity upon each of these main groups of co-morbidities.

Cardiovascular diseases (hypertension, myocardial ischaemia, and other types of heart disease)

In the analysis of Kitahara et al. (2014), the rubric "heart disease" includes International Classification of Diseases ICD-10 items 100-109, 111, 113, and 120-150. Thus, it covers hypertensive diseases of the heart and kidneys, ischaemic heart disease, and other types of heart disease. Cerebrovascular disease, arterial vascular disease and other disorders of the circulatory system are treated separately; they make a smaller contribution tom total mortality, and are affected less by concurrent obesity (Table 10).

Hypertension. Although essential hypertension is a frequent clinical diagnosis, particularly in older people, it usually does not in itself have a major impact upon life expectancy or quality-adjusted life expectancy. Thus, in the analysis of Kitahara et al. (2014), it was not listed as a cause of death for any of the men, and in the women there were only 3.3 and 4.1 age-adjusted annual deaths per 100,000 in normal weight and grossly obese individuals respectively.

Hypertension is important mainly as a precipitator of strokes, other circulatory problems and chronic renal disease. However, both systolic and diastolic blood pressures show significant correlations with BMI (Kotsis et al., 2005), being correlated particularly closely with the central type of obesity. Obese individuals have an increase of fatty tissue in their vascular walls, increasing vascular resistance and thus blood pressures. This in turn increases the work that the heart has to perform in pumping blood around the circulation, and it often results in left ventricular hypertrophy (Schmieder and Messerli, 1993).

Table 10: Impact of Class III obesity upon age-specific mortality (deaths per 100,000) and hazard ratios for premature death from specific categories of chronic disease over a 10-year average follow-up (comparison of BMI 18.5-25 and 40-59 kg/m^2). Based on data of Kitahara et al. (2014).

Condition	Males			Females		
	Normal (deaths)	Class III (deaths)	Class III (hazard ratio)	Normal (deaths)	Class III (deaths)	Class III (hazard ratio)
Heart Disease	98.5	337.2	3.38	112.0	244.8	2.19
Malignant neoplasms	135.1	171.8	1.27	112.0	174.3	1.56
Diabetes mellitus	5.3	58.5	11.0	4.3	32.5	7.60
Cerebro-vascular disease	33.1	22.4	0.69	33.1	47.2	1.43
Influenza & pneumonia	14.9	24.9	1.67	10.4	11.6	1.12
Chronic resp. disease	4.3	32.4	7.53	5.5	8.9	1.63
Chronic liver disease	12.1	10.6	8.76	1.8	7.2	4.00
Chronic renal disease	23.3	25.8	1.11	2.7	20.7	7.67
Accidents				13.7	22.9	5.96

Pathology. Obesity-related hypertension is marked by an activation of both the sympathetic nervous system and the renin-angiotensin system, with a resultant sodium retention. Factors that upset the normal relationship between blood pressure and sodium excretion include not only activation of the renin-angiotensin system, but also structural changes in the kidneys, hyperinsulinaemia, and stimulation of the sympathetic nervous system by an increased release of adipokines such as leptin from fat cells (Bravo et al., 2006; Re, 2009).

Epidemiology. Possible factors leading to an association between obesity and hypertension are summarized in Table 11. Individual authors have adopted slightly differing definitions of hypertension, but in general their conclusions have been concordant in showing an association between resting blood pressures and obesity. Wang et al. (2014) examined this relationship in a sample of 1870 Chinese adults (Table 12). Substantial gradients of multivariate adjusted odds ratios for hypertension were shown with respect to both BMI and waist circumferences, and a 2-way classification of waist circumferences (< or >85 cm, M; <or >80 cm, F). The authors

Table 11: Factors leading to an association between obesity and hypertension (Landsberg et al., 2013).

- Central abdominal obesity leads to insulin resistance, hyperinsulinaemia and increased blood leptin levels
- Increased sympathetic nerve activity increases the secretion of insulin, leptin and renin
- The activity of the angiotensin-renin system is increased, due to the sympathetic induced release of renin, angiotensinogen secreted by adipocytes and the stimulation of aldosterone secretion by adipocytes
- Salt reabsorption is increased due to sympathetic activity, an altered intra-renal distribution of blood flow, and altered blood levels of angiotensin, aldosterone and insulin.

of this report commented further that hypertension was related to both general and abdominal obesity, although the association was closer for general obesity (as indicated by BMI) than for an abdominal accumulation of body fat (as indicated by a large waist circumference)(Wang et al., 2014).

Data from the 1999-2000 US NHANES cross-sectional survey of 4805 adults aged > 18 years showed a 42.5% prevalence of hypertension (blood pressure >140/90 mm Hg) in those who were obese, compared with a prevalence of 27.8% in those who were overweight and 15.3% in those with a BMI < 25 kg/m^2 (Wang and Wang, 2004).

Likewise, prospective data from the Framingham Heart Study over a follow-up that was sometimes as long as 44 years showed that after adjusting data for age, smoking, diabetes and hypercholesterolaemia, the relative risk of developing hypertension in individuals with a BMI > 25 kg/m2 was 1.48 in men and 1.70 in women (Wilson, D'Agostino, and Sullivan, 2002), with respective risks increasing to 2.23 and 2.63 in those men and women with a BMI > 30 kg/m^2.

A meta-analysis based on 4 studies found that in men the incidence risk ratio for hypertension was 1.28 in those who were overweight and 1.84 for those who were obese, with corresponding ratios of 1.65 and 2.42 for women (Guh et al., 2009).

Increases of blood pressure have also been associated with increases of body mass over time. In adults (initially aged 25 years) who were followed for 15 years, a substantial increase of blood pressure was observed in those members of the group who allowed their BMI to increase by > 2 kg/m^2 (about a 5% increase of body fat content)(Lloyd-Jones et al., 2007). In such men, systolic blood pressures increased by an average of 0.38 mm Hg/year, and diastolic pressures by 0.61 mm Hg/year (a total effect of some 6/9 mm Hg). Likewise, in women, there were increments of 0.83 and 0.68 mm Hg/year (a total effect of around 12/10 mm Hg). Similarly, in a sample of 2194 Australian children an increase of BMI between the ages of 5 and 14 years was associated with higher final blood pressures (increments of some 5 mm Hg in both systolic and diastolic readings) relative to those seen in children who maintained a constant or decreasing BMI over the 9-year study (Mamum et al., 2005).

Quality of life. In its early stages, hypertension has little impact upon the quality of life, but if untreated many of the

Table 12: Multivariate adjusted* odds ratios for hypertension in relation to quartiles of BMI and to a 2-way classification of waist circumferences. Based on the data of Wang et al. (2014). In this study, hypertension was defined as a systolic pressure > 140 mmHg, a diastolic pressure > 90 mm Hg, and/or the self-reported use of anti-hypertensive medication.

Men		Women	
BMI (kg/m^2)	**Odds ratio**	**BMI (kg/m^2)**	**Odds ratio**
<18.5	0.75	<18.5	0.62
18.5-24.0	1.00	18.5-24.0	1.00
24.0-28.0	1.85	24.0-28.0	1.96
>28.0	3.42	>28.0	4.06
Circumference (cm)		**Circumference (cm)**	
<85	1.00	<80	1.00
>85	2.33	>80	2.49

*Data adjusted for age, smoking, alcohol consumption and educational attainment

long-term complications can cause a poor quality of life (Soni et al., 2010) due to renal complications, dyspnoea, chest pain, pre-syncope, palpitations and headache. If the SF-36 survey is used, much of the impact of obesity is upon the physical domain, with problems in walking, physical symptoms, vitality and (in older individuals) ability to attend to personal needs.

A comparison between healthy Brazilians and 246 patients undergoing treatment for hypertension found the latter to have poorer scores in 7 of 8 SF-36 domains (de Carvalho et al., 2013), although effects were again more marked in physical than in mental categories (Table 13); this group were mostly older individuals, with an average age of 61.5 years, and all of the hypertensive patients were attending regularly for medical treatment. A further study of 200 Brazilians with hypertension used a quality of life questionnaire specifically adapted to hypertension (Soutello et al., 2015), this again showed significant deteriorations in quality of life, scores being lower in those with more symptoms (renal damage, dyspnoea, chest pain, pre-syncope, palpitations and headache). Equally, application of the SF-36 survey to 1224 Chinese adults showed that hypertension was associated with significantly reduced scores on all 4 physical and two of the four mental scales (Xu et al., 2016) although perhaps because of a younger age range (45-53 years), the average adverse effect of hypertension (an SF-36 score averaging 94% of control) was smaller than in the study of de Carvalho and colleagues (2013). The Chinese study included a 2-level classification of physical activity; a relationship was found between educational attainment and higher SF-36 scores, and it was speculated that this may have been mediated by differences in habitual physical activity.

Ischaemic heart disease. The analysis of Kitahara et al. (2014) showed a substantial effect of gross obesity upon the loss of life from "ischaemic heart disease;" this rubric comprised items 120-125 in the International Classification of Diseases (angina, myocardial infarction and its complications, and other forms of acute and chronic ischaemic heart disease). Over the 10-year follow-up, respective age-adjusted annual deaths per 100,000 people were for normal weight men and women 98.3 and112.0, as compared with 337.2 and 244.8 for those with Class III obesity.

Pathology. In terms of the underlying pathology, a study of 6814 apparently healthy adults aged 45-84 years (Burke et al., 2008) looked for an increased in

Table 13. Effects of hypertension on SF-36 scores (based on the data of de Carvalho et al. 2013).

SF-36 dimension	Normal subjects	Hypertensive patients	Relative quality of life
Functional capacity	81	61	75%
Physical aspect	91	73	74%
Pain	76	61	80%
General health status	76	64	84%
Vitality	62	56	90%
Social aspect	73	62	85%
Emotional aspect	81	75	93%
Mental health	79	67	84%
Average	88	78	84%

various markers of subclinical cardiovascular disease in those who were obese. It found that obese individuals had several pathological markers, including increased coronary artery calcium content (+17%), an increased thickness of the intimal media in the internal carotid (+32%) and the common carotid artery (+45%) and a 2.7-fold increase of left ventricular mass.

Epidemiology. A number of long-term studies have suggested that obesity increases the risk of both non-fatal and fatal cardiovascular events. In Britain, a 20-year prospective study of 7176 men initially aged 40-59 years showed a multivariate-adjusted risk of major cardiovascular disease of 24.9/1000 in those who were obese (BMI >30 kg/m^2), compared with 13.9/1000 in those with a normal body mass (Wannamethee et al., 2005). Adverse findings were also associated with an increase of body mass, and a reduction of risk was seen with loss of weight over the course of the study. Study participants were classified by their smoking habits, but unfortunately this study took no account of habitual physical activity.

In an analysis of age-adjusted data for the Framingham population, Wilson et al. (2002) looked at the relative risks and population risks of developing various cardiovascular diagnoses (Table 14). Prospective data were collected over a follow-up that was sometimes as long as 44 years. The multivariate-adjusted relative risk of new cardiovascular events (angina pectoris, myocardial infarction, coronary heart disease and stroke) was increased by a factor of 1.48 for overweight and 1.70 for obese men, and by 2.23 for overweight and 2.63 for obese women (Wilson et al., 2002). The data were adjusted for age, smoking, diabetes, and hyper-cholesterolaemia, but again inter-individual differences in habitual physical activity were not considered. The findings suggested that overweight was responsible for 18% of the population risk of developing angina pectoris, 12% of the risk for myocardial infarction, 15% of the risk for "hard" coronary heart disease, 12% of the risk for cerebro-vascular disease and 2% of the risk for cardiovascular deaths, while (because of its lesser prevalence) obesity was responsible for 8, 2, 5, 8 and 0% of population risks for these same

Table 14: Age-adjusted associations of overweight and obesity with relative risk and population attributable risk of developing selected cardiovascular diagnoses. Based on data of Wilson et al. (2002) for participants in the Framingham Study.

Clinical outcome	Overweight		Obese	
	Relative risk	Added population attributable risk (%)	Relative risk	Added population attributable risk (%)
Angina pectoris	1.42	18	1.85	8
Myocardial infarction	1.22	12	1.19	2
"Hard" coronary heart disease	1.33	15	1,45	5
Cerebro-vascular disease	1.31	12	1.86	8
Total cardiovascular disease	1.21	10	1.46	5
CVD death	1.0	2	0.98	0

diagnoses. The limited impact of overweight and obesity on the number of cardiovascular and all-cause deaths seen in this study is a little surprising, and other investigators have found larger effects.

A prospective study of 1882 male employees at the Western Electric Company showed that a BMI of 30 kg/m^2 alone was associated with some increase in the relative risk of death from cardiovascular disease over a 24-year follow-up (1.16), and that this relative risk could be greatly exacerbated (to a value as high as 5.25) if there were also other risk factors, such as hypertension, high cholesterol levels and cigarette smoking (Stamler et al., 1993). Comparing individuals with and without hypertension, there was a clear stepwise increase of the risk of cardiovascular death in relation to BMI, even in those who were free of hypertension (Table 15). But, once again, the potential impact of differences in habitual physical activity does not seem to have been considered.

More recently, a study of 20,000 Dutch adults aged 20-65 years looked at the 10-year risk of non-fatal and fatal cardiovascular disease in relation to both BMI and waist circumference (Ineke et al., 2009). A BMI >30 kg/m^2 was associated with a two-fold increase in the risk of non-fatal and a four-fold increase in the risk of fatal heart attacks, with similar adverse effects from a waist circumference >102 cm in men or >88 cm in women; moreover, on the population level a seventh of non-fatal and a third of fatal heart attacks were considered as attributable to overweight or obesity. But yet again, this report did not consider the habitual physical activity of participants.

Analysis of 111,847 cases of non-ST segment elevation myocardial infarction (Madala et al., 2008) showed that the age of the first such incident decreased as relative body mass increased. Thus, the crude data indicated an average age of 74.6 years for the first incident in those with a BMI <18.5 kg/m^2, relative to 58.7 years for those with a BMI > 40 kg/m^2. After adjustment of the data for the use of medications and for several cardiovascular risk factors (but unfortunately not for habitual physical activity), the respective decrease in average age for the first incident of infarction, relative to the leanest individuals, was 3.5, 6.8, 9.4 and 12.0 years for individuals with BMIs in the ranges 25.1-30.0, 30.1- 35.0, 35.1-40.0, and > 40 kg/m^2.

***Importance of central versus peripheral fat accumulation*.** Where distinction has been drawn between central and peripheral adiposity, the risk of cardiovascular disease has generally been associated most closely with central fat deposition. A study of 4487 Australian women who were initially free of heart disease, diabetes and stroke (Goh et al., 2014) found that over a 10-year follow-up, several measures of central obesity (waist circumference, waist-to-hip ratio

Table 15: Risk of cardiovascular death (%) in relation to BMI and hypertensive status. Based on a 24-year follow-up of data of Stamler et al. (1993) for the Western Electric Company; note that no allowance was made for possible effects of habitual physical activity.

Hypertensive Status	BMI (kg/m^2)				
	<18.5	**18.5-24.9**	**25.0-29.9**	**30.0-34.9**	**>35**
No	3.5	6.3	10.4	14.7	14.5
Yes	16.3	16.3	20.8	26.4	29.3

and waist to stature ratio) were all better predictors of cardiovascular events than BMI. In terms of correlation coefficients, there was little to choose between the three indicators of central fat, but the waist-hip ratio had the possible advantage that it was less closely correlated with BMI. Correlations with the waist-to-stature ratio were 0.485 for cardiovascular incidents and 0.483 for cardiovascular deaths, as compared with 0.380 and 0.394 for correlations with BMI. Moreover, central obesity had a significant association with prognosis, even after adjusting statistically for BMI. Pischon et al. (2008) also noted that the overall risk of death remained correlated with BMI, even in statistical models that included waist circumference or waist-hip ratio as one of the variates.

The conclusions of Goh et al. (2014) reinforce findings from a somewhat similar investigation in Finland (Table 16). Pajunen and colleagues (2011) calculated the hazard ratios associated with 1 SD changes in BMI, waist circumference, waist/hip ratio, and an assessment of body fat content made by near-infra red reactance in a 9-year follow-up of 2842 men and 3196 women. In what was described as a "fully-adjusted" statistical model (allowance for total cholesterol, systolic blood pressure, smoking, diabetes and baseline cardiovascular disease, but not physical activity), all of the four measures of fat accumulation were associated with an increased risk of cardiovascular outcomes, but use of the near-infra red device did not add any new information to what could be inferred from simpler anthropometric measures of fat accumulation. Goh et al. (2014) suggested that central obesity is a marker of systemic inflammation, which predisposes to the risk of cardiovascular disease. Although abdominal obesity seems a significant predictor of future cardiac events, it should nevertheless be emphasized that in terms of practical policy, the respective impacts of diabetes mellitus and the metabolic syndrome upon cardiovascular risks are substantially larger than any measure of body fat (Wildman, et al., 2011).

A meta-analysis (Guh et al., 2009) looked separately at associations of coronary artery disease, congestive heart failure and stroke with markers of central fat accumulation. In eleven studies of coronary vascular disease, indices were based on both waist circumferences and

Table 16: Multivariate-adjusted* hazard ratios for coronary heart disease (CHD), ischaemic stroke, and all cardiovascular (CV) events over a 9 year follow-up, shown in relation to 1 SD changes in 4 measures of body fat (based on data of Pajunen et al., 2011).

Pathology	BMI	Waist circumference	Waist/hip ratio	% body fat (infra-red reactance)
CHD (men)	1.22	1.31	1.28	1.23
CHD (women)	1.45	1.55	1.56	1.50
Ischaemic stroke (men)	1.36	1.32	1.29	1.26+
Ischaemic stroke (women)	0.85+	1.00+	1.14+	0.86+
All CV events (men)	1.30	1.31	1.28	1.27
All CV events (women)	1.18	1.29	1.38	1.18+

+ Not statistically significant

*Data adjusted for systolic blood pressure, cholesterol, smoking, diabetes and baseline cardiovascular disease.

BMIs. Risk ratios in men were 1.41 and 1.29 for the 2 measures of overweight and 1.81 and 1.72 for obesity, with corresponding figures of 1.80 and 1.82 for overweight and 3.10 and 2.69 for obesity in women. In 4 studies of congestive heart failure, BMI data showed risk ratios of 1.31 (ns) for overweight and 1.79 for obesity in men and 1.27 (ns) for overweight and 1.78 for obesity in women. Pulmonary embolism was specifically identified in one study; this carried a risk ratio of 1.91 for those who were overweight and 3.51 for those who were obese. And in stroke, 7 studies showed average risk ratios of 1.23 for overweight and 1.51 for obesity in men, and of 1.15 for overweight and 1.49 for obesity in women.

Quality of Life. A heart attack has a considerable immediate impact upon an individual's quality of life, with complaints of breathlessness and thoracic pain, anxiety and depression, a loss of self-esteem, and a restriction of sexual activity (Westin et al., 1997). The quality of life improves gradually over a period of one year following the critical incident, but even then the normal quality of life is often not fully regained. Many investigators have looked at the effects of cardiovascular disease, using either individual items or composite scores for the SF-36 survey (Table 17), although it remains debatable whether either formulation of this questionnaire has tan appropriate sensitivity to detect the full impact of heart disease upon the quality of life (Spertus et al., 1994). Other options for such assessments include the Seattle Angina questionnaire (Cepeda-Valery et al., 2011) and the MacNew questionnaire (Dempster et al., 2004).

Although myocardial infarction can sometimes cause a short-term depression of mood state (Kavanagh et al., 1975), particularly if there is associated hypertension and angina, scores can return within the normal range if the patient is well educated and receives good social support (Muhammad et al., 2014). The "normative" data for patients with myocardial infarction presented in Table 17 were all collected within 1-6 months of the critical incident, but the effects (particularly on the composite mental scale) were very small. A formal comparison of patients seen immediately after myocardial infarction versus healthy controls, using the World Health Organization Quality of Life Questionnaire, demonstrated significant effects upon both physical and social domains, but reductions in scores for the psychological and environmental scales were insignificant, even at this stage (Table 18)(Srivastava et al., 2017).

When a sample of 6226 patients with coronary artery disease was followed longitudinally, the quality of life improved in most of the group, but about a quarter of the sample showed a decrease in their quality of life over a 5-year period; age, the level of social support and body mass index were among factors identifying

Table 17: Scores for the physical and mental components of the SF-36 quality of life measurement in 5508 adults with ischaemic heart disease. Based on the data of Huber et al. (2016).

Condition	Physical components scale	Mental components scale
Canadian norms	48	49
Myocardial infarction	43.5	47.9
Angina pectoris	38.5	47.2
Heart Failure	36.5	47.9

Table 18: Health-related quality of life, as measured by the World Health Organisation Quality of Life Questionnaire; comparison of data for healthy individuals with patients seen immediately following myocardial infarction (based on the data of Srivastava et al., 2017).

Domain	Physical	Psychological	Social	Environmental
Healthy subjects	25.5	21.6	10.0	27.1
Patients with myocardial infarction	21.1*	20.9	7.2*	26.9

* Statistically significant decrease

those individuals with an adverse trajectory (Sajobi et al., 2018).

Patients with stable coronary artery disease are likely to have greater anxiety than those with a myocardial infarction, affecting global, physical, social and emotional scores; further, those developing heart failure with dyspnoea are particularly vulnerable to depression (Morys et al., 2016).

***Influence of habitual physical activity*.** It has been known for many years that inadequate habitual physical activity can increase the risk of ischaemic heart disease. For example, Paffenberger et al. (1978) showed in an analysis of data for Harvard alumni that in those reporting a weekly energy expenditure of less than 8 MJ, there was a 64% increase in the risk of a heart attack. The relationship between obesity and an inadequate level of physical activity is equally well recognized. However, habitual physical activity seems to have been almost uniformly ignored as an important co-variate when examining the relationship between obesity and ischaemic heart disease. Plainly, there remains a need to repeat existing studies, performing analyses where the effects of obesity are examined independently of any associated differences in daily activity patterns.

Other types of heart disease. Items 126-151 on the International Classification of Diseases include pulmonary heart disease and problems of the pulmonary circulation, pericardial and endocardial disease, valvular problems, myocarditis, cardiomyopathies, electrical conduction disorders, arrhythmias and congestive heart failure. Taking this broad range of diagnoses as a group, and comparing individuals of normal body mass with those who are grossly obese, annual death rates per 100,000 were 23.1 vs. 150.1 in men and 19.5 vs. 76.6 in women (Kitahara et al., 2014).

The Framingham data showed a 4% increase in the risk of atrial fibrillation for each one-unit increase of BMI in a 13.7 year prospective comparison of obese subjects with those of normal body mass (Table 19). In a sample of 5282 people, the risk of atrial fibrillation, adjusted for cardiovascular risk factors and interim myocardial infarction or heart failure, but not for habitual physical activity, was 1.52 for men and 1.46 for women (Wang et al., 2004). The increased risk was apparently mediated by left atrial dilatation in those who were obese.

Table 19: Risk of incident atrial fibrillation in relation to an individual's obesity. Based on the age-adjusted data of Wang et al. (2004) over a 13.7-year follow-up period.

	Normal body mass	Overweight	Obese
Men	1.00	1.12	1.69
Women	1.00	1.20	1.59

In the case of congestive heart failure, Horwich et al. (2001) found that an association with obesity had little influence on the risk of premature mortality. However, a 26-year follow-up of 5209 patients from the Framingham cohort (Hubert et al., 1983) found that there was a statistically significant correlation between initial percentage of desirable weight and both angina and congestive heart failure (Table 20), with this risk being exacerbated by any subsequent weight gain. Over a 14-year follow-up, each unit increase of BMI increased the risk of heart failure by 5% in men and 7% in women. Another report, also based on data from the Framingham Study, found a doubling of the risk of heart failure in 55-year old individuals if they were obese (Kenchaiah et al., 2002). Even in young adults (average age 32 years), a finding of abnormal right ventricular morphology (increased ventricular mass, increased stroke volume and reduced ejection fraction) at echocardiography was 11.4% in those of normal body mass, but increased to 44.4% in those with a BMI of 30.0-34.9 kg/m^2, and 62.0% in those with a BMI of >35 kg/m^2 (Chahal et al., 2012). The adverse changes in right ventricular morphology are compounded by hormonal changes and an increased blood volume (Chahal et al., 2012). However, these consequences of obesity seem to have little adverse impact upon mortality-the so-called "obesity paradox."

An excessive accumulation of fat may also have an adverse effect upon electrical conduction within the heart. There is some evidence for a direct lipotoxic effect of fat upon the myocardium, and this is compounded by adverse effects from an increase of pro-inflammatory cytokines that damage endothelial function (Ebong et al., 2014).

Neoplasms

Obesity increases the risk of developing almost every type of cancer (Table 21). Kitahara et al., (2014) only calculated the overall impact of obesity upon deaths from neoplasms in women. Comparing the diagnoses D00-D48 for those of normal body mass with those who were grossly obese, the respective annual age-adjusted death rates were 2.9 and 14.7 per 100,000.

Pathology. It has long been recognized that an adequate level of regular physical activity is associated with a low risk of neoplasia at many body sites (Batty and Thune, 2000; Shephard and Shek, 1998).

Table 20: Multi-logistic regression coefficient linking initial relative body mass and cardiovascular issues over 26-year follow up. Based on the data of Hubert et al. (1983).

Event	Men	Women
Angina pectoris	.014$^+$	.007$^+$
Other coronary heart disease	.009$^+$	.010$^+$
Myocardial infarction	.006	.010$^+$
Death from coronary heart disease	.009$^+$	.010$^+$
Sudden death	.016$^+$	.010
Congestive heart failure	.014$^+$.	.015$^+$
Athero-thrombotic stroke	.004	.012$^+$
Death from coronary heart disease	.006	.008$^+$

* Data adjusted for age, systolic pressure, cholesterol, smoking, glucose tolerance, and left ventricular hypertrophy, but not for habitual physical activity. $^+$statistically significant relationship.

Table 21: Risk of incidence of various types of cancer in overweight and obese individuals relative to those of normal body mass, with assessments of fat accumulation made by both waist circumferences and BMIs. Based on data of Guh et al. (2009).

Type of tumour	Number of studies	Waist Circumference		BMI	
		Overweight	Obese	Overweight	Obese
Post-menopausal breast	3,15	1.13	1.30	1.08	1.13
Endometrial	2,12	1.15	1.42	1.53	3.22
Ovarian	1, 8	0.61	1.35	1.18	1.28
Colo-rectal (F)	4, 13	1.25	1.55	1.45	1.66
Colo-rectal(M)	5, 12	1.88	2.93	1.51	1.95
Renal	7, 7	1.37	1.90	2.06	2.32
Pancreatic	6, 10	1.30	2.52	1.24	1.59
Prostatic	0, 11			1.23	1.11
Oesophageal	1			1.14	1.21

Potential underlying mechanisms include a modulation of insulin-like growth factors, changes in cortisol and prostaglandin levels that enhance the cellular components of immune function, and a suppression of the gonadotrophic axis. Further, active individuals are not usually smokers, and an above average socioeconomic status tends to reduce the exposure of such individuals to airborne carcinogens.

Many of these factors operate in the inverse sense for those who are obese. The susceptibility to cancer typically shows a U-shaped relationship to body mass index, since smokers couple an increased susceptibility to cancer with a low body weight. In the case of breast cancer, one of the more important adverse factors in those who are obese is an increased synthesis of growth-promoting oestrogens in adipose tissue (Cleary and Grossmann, 2009). An increased adipose tissue synthesis of growth-promoting factors such as leptin, adiponectin, and testosterone is also a common thread predisposing to an increased risk for many types of cancerous lesion in those who are obese (Pischon et al., 2006a,b). Moreover, the adverse impact of obesity on the morphology of major organs (for example, the development of fatty infiltration and cirrhosis in the liver) increases local vulnerability to neoplastic change.

Epidemiology. In addition to reports on the overall risk of cancerous change, several investigators have focused on the relationship between obesity and the appearance of neoplasms at specific sites, including the colon, the prostate, the breasts and the kidneys. Because of their prevalence in the general population, and the increase in risk with obesity, the first three types of lesion have the largest population impact in terms of an obesity-induced shortening of lifespan.

All-cause cancers. Numerous reports have underlined a substantial overall impact of obesity upon cancer mortality. A 16-year prospective study of some 900,000 subjects, conducted by the American Cancer Society (Calle et al. 2003) found that after adjusting for many variables, including age, education, smoking, marital status, race, aspirin use, fat and vegetable consumption, and most

notably habitual physical activity (albeit using a crude four category scale), the relative risk of mortality from all- types of cancer increased significantly with BMI. When compared to individuals with a normal body mass, respective average risk ratios of 1.09, 1.20 and 1.52 were found for BMI ranges of 30.0-34.9. 35.0-39.9 and > 40 kg/m^2. This study also reported significantly increased death rates from cancer at individual sites in individuals with a BMI in the range 30-34.9 kg/m^2 (relative risks were for the oesophagus 1.28; for the colon and rectum 1.47; for the liver 1.90; for the gallbladder 1.76; for the pancreas 1.49; for the kidney 1.36; for non-Hodgkin's lymphoma 1.56; and for multiple myeloma 1.37).

In Britain, a massive cross-sectional study of 5.24 million individuals looked at relationships between BMI and the incidence and mortality from various types of cancer (Table 22). After adjusting data for sex, menopausal status, smoking, and age, but not for physical activity, significant increases of risk ratios were shown for each 5 kg/m^2 increase of BMI in many of 22 individual cancers; ratios were increased with respect to cancers of the uterus (1.62), gallbladder (1.31), kidney (1.25), cervix (1.10), thyroid (1.09) and leukaemia (1.09)(Bhaskaran et al., 2014), and associations with BMI were also shown for tumours of the liver (1.19), the colon (1.10), the ovaries (1.09) and the breasts (post-menopausal women, 1.05) (Bhaskaran et al., 2014).

Another large study in Britain (Reeves et al., 2007) followed 1.2 million women for cancer incidence (5.4 years), and cancer mortality (7 years). In addition to an increase of all-cause cancers in those who were obese, there were significant increases of risk in 10 of the 17 most common individual types of cancer. Data were adjusted for age, geographical region, socioeconomic status, age at first birth, parity, smoking status, alcohol intake, physical activity (a single question, based on participation in strenuous physical activity more than once a week), years since menopause, and use of hormone replacement therapy. For each 10 unit increase of BMI, the respective incidence increments were for all-cause cancer 1.12, endometrial cancer 2.89, cancer of the oesophagus 2.38, cancer of the kidney 1.53, cancer of the pancreas 1.24, ovarian cancer 1.14, breast cancer (post-menopausal women) 1.40, colon and rectal cancers 1.61, and non-Hodgkins lymphoma 1.17). Further, obesity had a similar impact upon mortality rates.

Guh et al. (2009) completed an

Table 22: New cases of various types of cancer attributable to overweight or obesity in the U.K. over a calendar year. Based on the data of Bhaskaran et al., (2014).

Site of lesion	New cases per year in U.K.	Percent attributed to overweight and obesity	Cases attributed to obesity
Breast	39,812	5.1	2035
Colon	26,725	11.1	2970
Kidney	9,369	16.6	1597
Uterus	8,288	40.8	3384
Leukaemia	8,257	6.3	522
Ovaries	7,011	7.3	512
Liver	4,241	15.6	661
Cervix	2,851	7.5	214
Thyroid	2,654	1.9	51
Gallbladder	660	20.3	134

extensive meta-analysis of the unadjusted risks of developing various types of cancer, based on both waist circumference and BMI assessments of overweight and obesity. A significant and substantial risk was shown for lesions at many sites, in general with rather similar conclusions being drawn from the two indices of obesity. Another meta-analysis, conducted by Dobbins et al. (2013) noted significant risk ratios in obese men for tumours of the colon (1.57), kidneys (1.57), gallbladder (1.47), pancreas (1.36), and malignant melanomas (1.26), while in obese women significant risk ratios were seen for esophageal adeno-carcinoma (2.04), endometrial cancers (1.85), gallbladder (1.82), kidneys (1.72), pancreas (1.34), leukemia (1.32), postmenopausal breast cancers (1.25), and colon cancers (1.19).

Colon cancers. Colon cancers account for the largest single number of obesity-related tumours (Table 22). An 18-year prospective study of 46,349 male health professionals found that after adjusting for numerous covariates, including a cumulative measure of habitual physical activity (MET-hours per week, derived from a questionnaire), there was some increase in the risk of colon cancer as soon as the BMI exceeded 22.5 kg/m^2 (a multivariate adjusted hazard ratio of 1.40). The hazard ratio increased further to 1.64 in those who were classed as overweight, and the greatest effect (a hazard ratio of 2.29) was seen with a BMI > 30 kg/m^2 (Thygesen et al., 2008). Moreover, in those who had decreased their weight by at least 4 kg over the course of the study, the hazard ratio dropped to 0.82, whereas in those who had gained more than 7 kg it was 1.46.

In Europe a 6.1-year study of 368,000 men and women found a significant relationship between obesity and colon cancer in men, but not in women (Pischon et al., 2006a,b), after adjusting data for smoking status, education, alcohol consumption, physical activity (summer and winter questionnaires, covering both recreational and household activities), menopausal status, and hormone replacement therapy. Comparing men in the highest BMI quintile (>29.4 kg/m^2) with those in the lowest quintile (<23.6 kg/m^2), the relative risk of colon cancer was 1.55. Others, also, have noted that obesity has a greater effect on the risk of colon cancer in men than in women (Guh et al., 2009).

Breast cancers. The breast is another major source of cancer mortality in women (Table 22). The impact of obesity upon the risk of breast cancer is most obvious in post-menopausal women who are not taking hormone replacement therapy (Bean et al., 2016). There is some evidence that the breast tumours provoked by obesity are less aggressive in type than tumours with other antecedents. Nattenmüller and colleagues (2018) found that 1402 women from a general population of 18,812 people developed breast cancer over a 4.7 year follow-up.; among post-menopausal members of this group, the risk (adjusted for variables that included the number of full-term pregnancies, pill use, educational level, and smoking status, but not habitual physical activity) was 20% higher in those who were obese. In women from the Asia-Pacific region, a 5 kg/m^2 increase of BMI was associated with a 31% increase in the risk of breast cancer (Renehan et al., 2008; Wang et al., 2016).

Further, an analysis of 23,182 deaths among 213,075 cancer survivors showed that obesity worsened survival prospects

(Chan et al., 2014). Ten years following treatment, the risk of developing metastases was increased 46% in obese individuals (Rock et al., 2012).

Uterine cancers. According to a British survey, uterine cancers are a third type of tumour strongly linked to obesity (Table 22), and indeed the obesity epidemic seems one reason why the incidence of uterine tumours has continued to grow in recent years. A meta-analysis of 26 studies, completed by the American Institute for Cancer Research (Jackson, 2013) found that for every 5-unit increase of BMI, there was a 50% increase in the risk of developing endometrial cancer, with some acceleration of risk in gross obesity; further, there was also some increase in the risk of aggressive, non-endometrial tumours in those who were obese. In contrast, exercise was found to be protective in eight of nine studies of leisure activity, all 5 studies of occupational activity, and 3 of 5 studies of transportational activity; there were also an increase of risk that paralleled increases of sitting time. A 5 kg increase of body mass further increased risk by 16%.

Renal cancers. One evaluation from the U.K. found that renal cancer was the fourth most significant tumour in terms of obesity impact (Table 22). Pischon and colleagues (2006a,b) suggested that renal cancer was significantly associated with obesity in women, but in men the only association of such tumours was with fat distribution, as evaluated by hip circumference. In women, adverse effects were associated with body mass, BMI, waist and hip circumferences; after adjustment of data for education, smoking, alcohol consumption, menopausal status, physical activity (as determined by summer and winter questionnaires, covering both recreational and household activities) and the use of hormone replacement therapy; the relative risk for the highest vs. the lowest BMI quintile was 2.25, and for the highest vs. the lowest waist circumference quintile was 2.98 (although the latter difference was no longer significant after accounting for the effects of body mass).

A more recent report agreed that for some reason the impact of obesity upon the risk of renal cancer was greater in women, but that a statistically significant increase of mortality could also be demonstrated in obese men (Wilson and Cho, 2016). Suggested mechanisms include an increase of insulin resistance, and increased levels of certain growth factors including insulin-like growth factor, sex steroids, and biochemical markers of inflammation such as adiponectin.

Prostate cancers. Prostate cancers are common in older men, but the reported modification of risk by obesity has sometimes been quite small. One study looked at the incidence of prostate cancer in 69,991 men. After adjusting data for age, race, education, family history, energy intake, smoking, PSA testing, diabetes and physical activity (a five category questionnaire assessment of recreational energy expenditures), rate ratios for low grade non-meta-static, high grade non-metastatic and metastatic lesions in those who were obese were, respectively, 0.84, 1.22 and 1.54 relative to individuals with a normal body mass (Rodriguez et al., 2007). Moreover, those individuals who lost 5 kg over a 10-year follow-up had a reduced risk of developing high-grade non-metastatic cancer (relative risk of 0.58 in those

losing weight).

In another report, a 5-6 year follow-up of 287,700 U.S. men showed that after adjusting for age, race, smoking status, education, history of diabetes and family history, a BMI >25 kg/m^2 gave a relative risk of mortality from prostate cancer of 1.25, a BMI > 30 kg/m^2 a risk of 1.46, and a BMI > 35 kg/m^2 a risk of 2.12 (Wright et al., 2007).

Quality of life. In addition to causing an early mortality, many types of tumour have a major impact upon long-term quality-adjusted life expectancy. Indeed, for a large proportion of patients, the loss of quality-adjusted years may be at least as important as the decrease in survival prospects. For example, the otherwise successful treatment of prostate tumours is often accompanied by persistent urinary and/or faecal incontinence, surgical treatments of colo-rectal cancers may require the collection of faeces in disposable bags for the remainder of the patient's life, and the self-confidence of most women is affected by surgical mastectomy and/or irradiation induced loss of hair. Many people also come to dread long weeks of attendance at centres for tumour irradiation. Anaemia is a further important issue for many people, leading to early fatigue and difficulty in performing physical work (Cella, 1998). Conversely, there is growing evidence that the quality of life of many patients can be enhanced by participation in exercise programmes after immediate treatment of the tumour (Mishra et al., 2012).

A study from India found that 82% of 768 cancer patients had a low quality of life score (Nayak et al., 2017). Another report (Hydarnejad et al., 2011) applied the European Organization for Research and Treatment of Cancer QoL Questionnaire (EORTC QLQ-C30) to 200 patients who were receiving chemotherapy; the score was "fairly favourable" in 66% of this group. Factors affecting patient responses were fears about the future (29%), thinking about the disease and its consequences (26.5%), impatience (24%), and depression (17.5%). Application of a validated Dutch version of the SF-36 survey to cancer patients in the Netherlands found some reduction of score in most of the 8 domains (Aaronson et al., 1998) (Table 23), but by far the largest adverse effect was for "role physical."

Table 23: Quality of life as assessed by the SF-36 survey in 435 patients with cancer who were undergoing active treatment, and a sample of the general Dutch population. Based on data of Aaronson et al. (1998).

Factor	Normal Dutch adults	Cancer patients	Ratio
Physical function	83.4	63.6	0.76
Role physical	76.4	35.0	0.46
Bodily pain	74.9	69.3	0.92
General health	70.7	52.5	0.74
Vitality	68.6	60.1	0.88
Social functioning	84.0	73.9	0.88
Emotional health	82.3	58.4	0.71
Mental health	76.8	68.0	0.86

Interactions of obesity with habitual physical activity. We have noted above that inadequate physical activity could compound and/or confound the influence of obesity upon the risk of neoplasms. As noted above, a number of epidemiological reports on cancers at specific sites have included a measure of habitual physical activity, but, this has been less common when assessing the impact of obesity upon cancer risks as a whole, exceptions

being Calle et al. (2003) and Rodriguez et al. (2007). Moreover, because of large subject numbers, even when habitual physical activity has been considered, the measures used have been relatively weak (and correspondingly unlikely to attract all of the variance that should have been attributed to this factor).

Type 2 Diabetes mellitus and metabolic syndrome

Most of the added mortality in this category of chronic disease is attributable to diabetes mellitus (International Classification of Diseases 10, Codes E10-E14). Some deaths are also ascribed to overweight and obesity (E66), but the metabolic syndrome is not specifically listed as a cause of death in the analysis of Kitahara et al. (2014).

Diabetes mellitus. An accumulation of body fat, as shown by a high body mass index, is a dominant risk factor for Type 2 diabetes mellitus.

Pathogeneis*.* The endoplasmic reticulum is an element of cell structure responsible for the folding and trafficking of protein molecules (Ron and Walter, 2007). This structure is critical to many metabolic functions, and it may be implicated in the association between obesity and an increased risk of diabetes mellitus. Investigators have argued that a high fat diet and/or an increase in body mass lead to increased protein metabolism, with a stressing of the endoplasmic reticulum, an inflammatory response, and a resultant suppression of normal protein folding both in metabolically active tissues such as the liver and in fat cells (Hotamisigil, 2010; Wang and Kaufman, 2016), possibly with involvement of a TNF-alpha receptor (Hotamisligil, 1999).

The inflammatory response in turn causes serine phosphorylation and a suppression of insulin receptors on the surface of muscle and liver cells, creating the classical harbingers of diabetes mellitus- insulin resistance and a high blood glucose level. There may also be an increase in hepatic gluconeogenesis (Martyn, Kaneki, and Yasuhara, 2014). Typically, the progression to clinical diabetes mellitus occurs over a number of years, reflecting a diminishing ability of the pancreatic beta cells to maintain a high enough rate of insulin secretion to compensate for the growing insulin resistance (Scheen, 2000).

Epidemiology. Epidemiological studies have shown a strong and consistent relationship between obesity and the development of diabetes mellitus, although not all of these analyses have co-varied for the potential role of habitual physical activity in this process.

A systematic review of 89 studies found that the development of type 2 diabetes mellitus was the most common among 18 adverse health consequence of becoming obese. In men with a BMI > 30 kg /m^2, the average risk across these studies was increased seven-fold relative to those with a BMI<25 kg/m^2, and in women, the risk was increased twelve-fold by a similar increase of BMI (Guh et al., 2009).

The high risk that obese individuals will develop diabetes is well illustrated by a 14-year follow-up of 114,281 nurses initially aged 30-55 years (Table 24). A total of 2204 cases of diabetes mellitus developed over the course of this survey. The data were statistically adjusted only for age, and on this basis the lowest risk was seen in those with a BMI <22 kg/m^2. The risk ratio rose progressively with greater degrees of adiposity, to reach a dramatic 93-fold increase in those with an

Table 24: Age-adjusted relationship between BMI (based on a *reported* height and body mass) and relative risk of developing type 2 diabetes mellitus over the course of a 14-year follow-up. Based on the age-adjusted data of Colditz et al. (1995) for 114,281 female nurses initially aged 30-55 years.

BMI (kg/m²)	<22	22.0-22.9	23.0-23.9	24.0-24.9	25.0-26.9	27.0-28.9	29.0-310,9	31.0-32.9	33.0-34.9	>35.0
Relative risk of diabetes*	1.0	2.9	4.3	5.0	8.1	15.8	27.6	40.3	54.0	93.2

*Age-adjusted data

initial BMI >35 kg/m² (Colditz et al., 1995). In this analysis, even a BMI in the range 22-25 kg/m2, often considered as acceptable or in the ideal range, led to a considerable increase in the risk of developing diabetes relative to those with a BMI < 22 kg/m². An increased risk was also seen in those who had allowed their body mass to increase since the age of 18 years. Even a modest increase in weight over this period (5-8 kg) was enough to double the risk, and a gain of 20 kg was associated with a 12-fold increase in the risk of developing type 2 diabetes.

A 10-year follow-up of 22,171 male health professionals initially aged 40-75 years further underlined the adverse metabolic consequences of fat accumulation (Koh-Banerjee et al., 2004). For every kg of body mass participants had gained since the age of 21 years, their risk of developing type 2 diabetes mellitus was increased by 7% (Table 25). As in the study of female nurses, even men with BMI values in the commonly accepted optimal range (22-25 kg/m²) had a substantially higher risk of developing diabetes (risk ratio 1.2 -1.5) than individuals with BMI values < 21 kg/m². The adverse prognosis was increased progressively by any weight gain since the age of 21 years. A multivariate adjusted risk ratio for diabetes mellitus allowed statistically for a family history of diabetes, smoking and alcohol consumption, dietary fibre intake, baseline anthropometric characteristics, and a quintile categorization of questionnaire assessed active energy expenditures per week. Risk ratios were 2.6 for those with a BMI in the range 25-30 kg/m², and 4.9 for those with a BMI > 30 kg/m². Further, even after controlling for their overall gain of body mass, men who accumulated a substantial amount of abdominal fat, as shown by a 14.6 cm increase in their waist circumference, had a 1.7-fold increase in their risk ratio for diabetes mellitus. In all, 56 % of the cases of diabetes in this cohort could be attributed to an increase in body mass > 7 kg, and 20% were associated with a waist circumference increase >2.5 cm.

Finally, a meta-analysis of nine studies (Guh et al., 2009) found diabetes incidence risk ratios of 2.40 for

Table 25: Relationship between change of body mass since the age of 21 years and risk of diabetes mellitus, as seen in a study of 22,171 male health professionals initially aged 40-75 years (Koh-Banerjee et al., 2004).

Change of body mass since age 21 years	Loss>3kg	-2 to+ 2 kg	Gain 3-6 kg	Gain 7-11 kg	Gain 12-18 kg	Gain >19 kg
Risk ratio*	0.4	1.0	1.8	2.1	3.0	8.8

*Risk ratio adjusted for cigarette and alcohol consumption, physical activity, family history of diabetes, dietary fibre intake and BMI at age 21 years.

overweight and 6.74 for obese men, and 3.92 and 12.41 as corresponding figures for overweight and obese women.

Quality of life. The quality of life of the diabetic patient is adversely affected by the ever-present need to monitor diet and blood sugar levels, even in the early stages of the condition. Many of the subsequent complications such as coronary arterial disease, renal failure, disturbances of vision, micro- and macro-vascular disease, impaired sexual function and eventual mental deterioration lead to substantial reductions in the quality of life for the affected patient (Trikkalinou et al., 2017). In general, formal measurements have looked at the health-related, rather than the overall quality of life; this distinction is important in diabetes, since attempts to improve health by rigid control of blood sugar levels can worsen rather than improve the overall quality of life (Catalano et al., 2004; Singh and Bradley, 2006).

Dhana et al. (2016) pointed out in a prospective study of Dutch citizens 55 years and older that in this age group obesity increased the number of years during which a person faced the reduced quality of life associated with living with type 2 diabetes mellitus (a 2.8 years impact in men, and 4.7 years women)(Dhana et al., 2016), with a corresponding increase in the burdens placed upon the medical system.

The perception of poor health in those over 70 years of age is systematically influenced by blood glucose status (Table 26). Complaints including headache, joint and chest pains, exercise dyspnoea, constipation, urinary incontinence, dizziness and fainting were all most frequent in those previously diagnosed with diabetes mellitus (Hiltunen et al., 1996).

Cost-utility analyses conducted on a variety of patients with type 2 diabetes yielded a coefficient of 0.601 if only dietary adjustments were required to control the disorder. However, there were much greater penalties if the disease had progressed to micro-vascular, neuropathic or cardiovascular complications (Coffey, Brandle, and Zhou, 2002). Utility values associated with these various complications are summarized in Table 27.

Interactions with physical activity. Physical inactivity is well-recognized as a risk factor for diabetes mellitus, but a study of 68,500 U.S. adults suggested that the adverse effects of obesity and a sedentary lifestyle were relatively independent of each other (Sullivan et al., 2005). In this study, physical activity was defined on a simple binary scale (active or not >30 minutes, 3 times per week). The risk of diabetes mellitus increased with obesity whether the individual was rated

Table 26: Perceptions of current health in individuals over 70 years of age, categorized by blood glucose status. Based on the data of Hiltunen et al.(1996).

Perceived health status	Established diabetes	Recently diagnosed	Impaired Glucose tolerance	Normal blood sugar
Good	10%	29%	27%	23%
Moderate	58%	51%	55%	60%
Poor	32%	20%	18%	17%

Table 27: Quality of Life utility values in type 2 diabetes mellitus with various co-morbidities. Based on the data of Coffey et al. (2002).

Patient Status	Added penalty	Mean utility value
Diabetes (diet-controlled, non-obese men)		0.601
Females	-0.038	
Obese	-0.021	
Oral anti-diabetic medication	-0.023	
Insulin treatment	-0.034	
Retinopathy-one eye blind	-0.043	
Retinopathy- two eyes blind	-0.170	
Diabetic renal disease	-0.011	
Dialysis required_	-0.078	
Neuropathic tingling	-0.060	
Neuropathy	-0.065	
Neuropathic sores	-0.099	
Amputation	-0.105	
Transient ischaemia or stroke	-0.044	
Persistent stroke effects	-0.072	
Congestive heart failure	-0.052	
High blood pressure	-0.011	

as physically active or not, and physical inactivity had an adverse effect upon risks at all levels of obesity (Table 28).

Metabolic syndrome. In general, the adverse consequences of the metabolic syndrome arise from its complications, rather than from the syndrome itself. The only component of the syndrome considered in the analysis of Kitahara et al. (2014) is overweight/obesity. The participants in their study with a normal body mass had an annual death rate of 0 per 100,000, whereas values for grossly obese men and women were 38.3 and 20.6 per 100,000, respectively.

History of the metabolic syndrome. The metabolic syndrome is a fairly recent diagnostic concept. A Marseilles physician named Jean Vague noted in 1947 that upper body obesity predisposed not only to diabetes mellitus, but also to atherosclerosis, gout and renal calculi (Vague, 1947). However, his paper was published in a French-language journal, and thus was not widely read, particularly in North America. Description of the phenomenon under the term *metabolic syndrome* did not enter English language texts until around 1977.

In that year, the German physician Haller (1977) described a combination of obesity with diabetes mellitus, hyperlipoproteinaemia, hyperuricaemia and hepatic steatosis as "*the metabolic syndrome.*" Another German investigator (Singer, 1977) adopted the same terminology to describe a combination of obesity, gout, diabetes mellitus, hypertension and hyperlipoproteinemia, while Phillips (1977) underlined the role of a combination of glucose intolerance, hyperinsulinaemia, hypercholesterolaemia, hypertriglyceridaemia and hypertension in the genesis of myocardial infarction.

The metabolic syndrome is now regarded as widely prevalent, affecting as many as a quarter of the world's population (Alberti et al., 2006), with numbers being largest for men aged > 40

Table 28: Prevalence of diabetes mellitus (%) in relation to obesity and habitual physical activity. Based on the data of Sullivan et al. (2005).

Condition	Activity level	Normal body weight	Overweight	Obese Class I & II	Obese Class III
Diabetes mellitus	Active	2.2	4.6	8.7	14.1
	Inactive	4.5	8.0	13.7	22.1

years (Ezquerra et al., 2008).

Diagnostic criteria. The metabolic syndrome is defined by the presence of at least three in a cluster of five cardiovascular risk factors: an intra-abdominal accumulation of fat; high serum triglycerides, low high density cholesterol levels, an elevated blood pressure and an elevated fasting blood glucose level. Individual expert groups have followed generally similar diagnostic principles, always including some measure of obesity such as BMI or waist circumference, but unfortunately there remain substantial inter-group differences in precise details of the diagnostic criteria (Table 29). For example, the WHO definition of the metabolic syndrome (Alberti and Zimmett, 1999) comprises diabetes mellitus, impaired glucose tolerance or insulin resistance and at least 2 other markers drawn from the following list: blood pressure >140/80 mmHg, dyslipidaemia [triglycerides >1.695 mmol/L, HDL cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women], central obesity [waist/hip ratio >0.90 in men or >0.85 in women, or BMI > 30 kg/m^2], or microalbuminuria [an urinary albumin excretion >20 mg/min, or an albumin/creatine ratio >30 mg/g]. In substantial contrast, the US National Cholesterol Education Program Adult Treatment Panel III (Expert Panel, 2001) requires at least three of the following criteria: a large waist circumference (102 cm in men or 88 cm in women), triglycerides > 1.7 mmol/L, a low HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), a high blood pressure (>130/85 mm Hg, or the prescription of treatment for hypertension), or a high fasting blood glucose (> 6.1 mmol/L).

Table 29: Criteria for diagnosis of the metabolic syndrome, as proposed by various expert bodies.

Expert Body	Obesity measure	Triglycerides	HDL Cholesterol	Blood pressure	Fasting blood glucose	Diagnostic criteria
IDF	Waist circumference (not needed if BMI > 30 kg/m^2)	> 1.7 mmol/L or specific treatment	<1.03 mmol/L (M) or<1.29 mmol/L(F) or specific treatment	Systolic > 130 or diastolic >85 mm Hg or specific treatment	> 5.6 mmol/L or diagnosis of type 2 diabetes mellitus	Central obesity + 2 other factors
WHO	Waist/hip ratio > 0.90 (M), > 0.85 (F) or BMI > 30 kg/m^2	>1.695 mmol/L	< 0.9 mmol/L M), < 1.0 mmol/L (F)	>140/90 mm Hg	Diabetes mellitus or impaired glucose tolerance or insulin resistance	Fasting blood glucose issue + 2 other factors, (including microalbuminuria
EGIR	Waist circumference > 94 cm (M), > 80 cm (F)	>2 mmol/L or treatment	< 1.0 mmol/L or treatment	>140/90 mm Hg or treatment	> 6.1mmol/L	Insulin resistance + 2 other factors
NCEP	Waist circumference > 102 cm (M), > 88 cm (F)	> 1.7 mmol/L	<1.03 mmol/L (M), < 1.29 mmol/L (F)	>130/85 mm Hg or treatment	>6.1 mmol/L	Any 3 of these factors
AHA	Waist circumference > 102 cm (M), > 88 cm (F)	> 1.7 mmol/L	<1.03 mmol/L (M), <1.29 mmol/L (F)	>130/85 mm Hg or treatment	> 5.6 mmol/L or treatment	Any 3 of these factors

Expert groups: IDF = International Diabetes Federation; WHO = World Health Organisation; EGIR = European group for study of insulin resistance; NCEP = National cholesterol education program; AHA = American Heart Association

Pathogenesis. In essence, the metabolic syndrome describes a clustering of abnormalities that are commonly associated with central obesity. The reason underlying the grouping of these abnormalities is unclear, but one probable factor is that obesity causes a low-grade general inflammatory reaction (Emmanuela et al., 2012; Esser et al., 2014).

Acceptance of the metabolic syndrome as a specific clinical entity, and its practical utility as a clinical tool remain somewhat controversial issues, with the differing diagnostic criteria proposed by various expert bodies hampering adoption of the idea (Kahn et al., 2005). Further, some investigators have argued that if due allowance is made for the dominant element of abdominal obesity, the clustering of other negative indices that would justify a diagnosis of the metabolic syndrome adds little to predicting the risk of cardiovascular disease (Kahn, 2008). Such critics have indeed claimed that the metabolic syndrome is no better than the fasting blood sugar as a means of predicting the risk of developing diabetes mellitus.

Epidemiology. It is generally agreed that the metabolic syndrome becomes much more marked as the level of obesity increases. One study of 19,593 Chinese children aged 6-18 years found an odds ratio of 67 for presence of the metabolic syndrome in those who were judged as overweight on the basis of their BMI, and an odds ratio of 250 for those who were obese (Chen et al., 2012). Moreover, the prevalence of the syndrome in this sample was 5 times greater in those with a combination of general and central obesity than in those with central obesity alone. A study of 1844 school children aged 7-14 years reported a prevalence of the metabolic syndrome of 2.3% in children that had a normal height and body mass, of 20.5% in those who were overweight, and of 33.1% in those who were obese (Liu et al., 2010). Although the metabolic syndrome is commonly linked to a diagnosis of diabetes mellitus, obesity is a predisposing factor in both diabetic and non-diabetic patients (Chen, et al., 2008).

Diagnosis of the metabolic syndrome has been associated with a 30% to 400% increase of cardiovascular risk, depending on the population studied and the duration of follow-up (Kahn et al., 2005). Examining data for a sample of 19,173 men, Katzmarzyk et al. (2005) demonstrated that relative to those who did not have the metabolic syndrome, the presence of this diagnosis increased all-cause mortality by 1.11 in those of normal weight, 1.09 in those who were overweight, and 1.55 in those who were obese. The adverse effect of fat accumulation upon mortality was even greater in those with cardiovascular disease, the corresponding odds ratios being 2.06, 1.83 and 2.33. However, after including a treadmill-time based assessment of cardio-respiratory fitness in the statistical model, the additional risk associated with presence of the metabolic syndrome was no longer statistically significant (Katzmaryzyk et al., 2004), underlining the value of an increase of habitual physical activity in the treatment of this condition.

As noted above, some have argued that the increase of cardiovascular risks and mortality associated with diagnosis of the metabolic syndrome are no greater than could have been predicted from an independent consideration of the individual factors that contribute to this diagnosis.

Interaction with physical activity. Based on the observations of Katzmarzyk et al. (2004, 2005), it might appear that a substantial fraction of the adverse prognosis commonly attributed to presence of the metabolic syndrome may in reality reflect a low level of aerobic fitness, and thus (presumably) a low level of habitual physical activity. However, this question merits further investigation. The method of assessing fitness used in these studies (treadmill running time) is unfortunately heavily dependent not only upon aerobic fitness, but also on the individual's body mass, and there thus is a need for more direct testing of possible relationships between habitual physical activity and the risks of the metabolic syndrome.

Cerebro-vascular disease and atherosclerosis stroke

In the analysis of Kitahara et al. (2014), cerebro-vascular disease comprised items 160-169 in the International Classification of Diseases. Surprisingly, the cerebro-vascular mortality per 100,000 for grossly obese men was lower than that for individuals of normal weight (22.4 vs. 33.1). However, in women, there was some adverse effect from fat accumulation (47.2 vs. 33.1 deaths per 100,000).

This assessment has been confirmed in other analyses, with obesity only having a significant adverse influence on the risk of cerebro-vascular disease when it is accompanied by hypertension, hyperlipidaemia or impaired glucose tolerance (Isozumi, 2004). However, a small study of 40-year-old Croatian men (Bosnar-Puretić et al., 2009) found a substantial difference of waist circumference between those suffering a stroke and controls (102.6 vs. 94.9 cm)**.**

Potential mechanisms linking obesity and the risk of a stroke include the adverse action of various adipokines such as adiponectin, leptin, resistin, apelin, and visfatin upon endothelial function (Letra and Sena, 2017). Cerebral blood flow is also reduced in obesity, and in older patients this may not only exacerbate the effects of stroke, but also predispose to senile dementia (Dorrance et al., 2014).

Digestive conditions

Abdominal conditions influenced by obesity include liver, pancreatic and gall bladder diseases. The analysis of Kitahara et al. (2014) focused upon liver disease (Items K70, K73, K74 in the International Classification of Diseases), finding that obesity had little effect on mortality from hepatic conditions (death rates of 10.6 vs.12.1 per 100,000 in normal weight men, and of 7.2 vs. 5.4 per 100,000 in normal weight women).

Non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease (NAFLD) is a condition marked by an excessive accumulation of fat in the liver, without evidence that the affected individual has habitually consumed an excessive amount of alcohol. The liver cells of a healthy individual normally contain some fat, but NAFLD is diagnosed when the average hepatic fat content exceeds 5% of the total tissue mass. Diagnosis is currently based on proton magnetic resonance spectroscopy or CT scan assessments of liver fat content. The condition is closely related to obesity; some 75% of obese people have a fatty liver, and about 35% of these patients progress to NAFLD (Bellentani et al., 2000; Hamaguchi et al., 2005). Nevertheless, the condition is commonly accompanied by diabetes mellitus and cardiovascular disease, and obesity is only one of several factors contributing to the development of

Table 30: Relationship between an individual's quartile of waist circumference and the hazard ratio for NAFLD as seen in a multivariate analysis. Based on the data of Yun et al. (2016).

Men		Women	
Waist circumference quartile	Multivariate hazard ratio*	Waist circumference quartile	Multivariate hazard ratio*
< 76 cm	1.00	<66.5 cm	1.00
76.1-80.3	1.50	66.6-70.6	1.43
80.4-84.8	1.68	70.7-75.0	2.19
>84.9	1.81	>75.1	2.63

*Model adjusted for age, smoking status, alcohol intake, regular exercise, educational level and body mass index.

NAFLD.

Pathology. As NAFLD progresses, large vacuoles of triglycerides accumulate in individual liver cells, and this process is often accompanied by an inflammatory reaction (steato-hepatitis). Unless treated successfully, the liver pathology can progress further to hepatic fibrosis, cirrhosis and occasionally hepatic carcinoma (Shephard and Johnson, 2015).

The overall process reflects one or more defects in fat metabolism. Potential factors include an increased delivery of fatty acids to the liver, either from adipose tissue or directly from the diet, an increased hepatic lipogenesis, a decreased hepatic oxidation of fatty acids, and a decreased release of fatty acids from the liver. The first of these mechanisms is thought to be the dominant in the genesis of NAFLD (Katsanos, 2004). There is commonly an accompanying insulin resistance, both in the liver and in adipose tissue.

Epidemiology. NAFLD is closely associated with obesity, and in particular with the central type of central obesity. A cross-sectional analysis of data for 37,130 Korean men and women (Yun et al., 2016) showed a substantial dose-response relationship between NAFLD and one measure of central adiposity (waist circumference), even after making allowance for other potential causal factors including a high BMI and a lack of exercise (Table 30). Moreover, over a 2-year follow-up of this particular population, the incidence of NAFLD was significantly lower in those whose waist circumference had remained constant or decreased relative to those whose waist circumference had increased (Table 31).

Multiple regression analysis of data for 6511 elderly Taiwanese (Shen et al., 2014) underlined that the two most important and independent partial correlates of severe NAFLD were central obesity (7.77), and a BMI > 25 kg/m^2 (6.97). Popova et al. (2012) again noted that NAFLD was related to BMI (prevalence with overweight, 6.7%, with grade I obesity 10.1%, with grade 2 obesity 14.3% and with grade 3 obesity 14.9%). Other investigators have also found associations of NAFLD with central obesity, as monitored by waist circumference, but the condition has been unrelated to levels of subcutaneous fat (Jakobsen et al., 2007).

A meta-analysis examined the independent contributions of waist circumference, waist-hip ratio and BMI to the risk of developing fatty infiltration of the liver (Pang et al., 2015). All reports

Table 31: Changes in waist circumference over 2 years of observation in relation to multivariate hazard ratios for NAFLD. Based on the data of Yun et al. (2016).

Men		Women	
Waist circumference change	Multivariate hazard ratio*	Waist circumference change	Multivariate hazard ratio*
< -2.0 cm	0.88	< -1.5 cm	0.82
-1.9 to - 0.5	1.00	-1.4 to +1.3	1.00
-0.6 to + 3.2	1.00	+1.4 to + 4.3	1.15
> +3.3	1.16	> +4.4	1.29

*Model adjusted for age, smoking status, alcohol intake, regular exercise, educational level and body mass index.

confirmed an adverse effect of fat accumulation upon risk. A high vs. a low waist circumference gave an average odds ratio of 2.34 in 7 studies, and a high vs. a low waist-hip ratio yielded an odds ratio averaging 4.06 in 3 studies, while the odds ratio was 2.85 in 5 comparisons of a low versus a high BMI. The implication of these statistics is that all 3 factors are indicative of risk, but that a person can have a relatively normal BMI, and still develop a fatty liver because of a central accumulation of body fat.

One analysis, based on 5052 men and women, calculated a fatty liver index, based on a combination of waist circumference, triglyceride levels and gamma glutamyl transferase levels (Mohamed et al., 2016). Although this index had an acceptable diagnostic sensitivity (82%) and specificity (77%), the authors of the report concluded that waist circumference alone was a simpler method of predicting the risk of developing a fatty liver, with about the same performance characteristics as the multivariate fatty liver index.

NAFLD in itself is not in itself associated with an increase in premature mortality (Lazo et al., 2011), but if unresolved, the cirrhosis may need treating by liver transplantation, and the condition can progress to a variety of potentially fatal outcomes, particularly decompensated cirrhosis and hepatic cancer (Nguyen et al., 2018).

Quality of life. NAFLD leads to a significant decrease in the patient's quality of life, most commonly associated with cirrhosis and complaints of fatigue (Assimakopoulos et al., 2018; Kennedy-Martin et al., 2018). Application of the SF-36 survey showed that adults without chronic illness had average composite scores of 55.8 (physical) and 52.5 (mental); in contrast, mean composite scores in those with NAFLD dropped to 45.2 (physical) and 47.6 (mental), falling further to 44.6 in those with moderate fibrosis, and to 38.4 in those with cirrhosis (David et al., 2009).

Interactions with physical activity. The risk of NAFLD is substantially reduced in active individuals (Shephard and Johnson, 2015), raising the issue as to how far the apparent linkage between obesity and poor liver health is attributable primarily to an inadequate level of habitual physical activity.

Pancreatic disease. Obesity is associated with an increased risk of developing acute and chronic pancreatitis, as well as an elevated risk of pancreatic cancers.

Acute pancreatitis. Obesity appears to augment the severity of acute pancreatitis, leading to more complications, prolonged hospitalization and an increased mortality from this diagnosis (Evans et al., 2010). Suggested mechanisms include a peri-pancreatic deposition of fat, liberation of adipokines, microvascular changes in the pancreas, and resulting areas of local necrosis. A meta-analysis of 5 studies found that relative to non-obese individuals, those who were obese had odds ratios of 2.9 for developing severe pancreatitis, 2.3 for having systemic complications of the disease, 3.8 for local complications, and 2.1 for mortality (Evans et al., 2010; Martinez et al., 2006).

Chronic pancreatitis. There is some evidence that an excessive body mass is also a frequent precursor of chronic pancreatitis (Kim and Han, 2012)**.** Chronic pancreatitis has a substantial influence upon the quality of life, particularly in young patients, with most of the adverse impact attributable to chronic pain (Pezilli et al., 2006).

Cancer of the pancreas. The risk of developing cancer of the pancreas is increased by 10% for a 5 kg/m^2 increase of BMI; suggested mechanisms have included hormonal and inflammatory effects of fat accumulation, increased exposure to carcinogens as food intake is increased, and inadequate habitual physical activity, with a sedentary lifestyle having at least a weak effect in increasing risk (Bracci, 2012). A meta-analysis demonstrated a relative risk of pancreatic cancer of 0.79 for those who engaged in regular moderate physical activity (O'Rorke et al., 2010). Obesity worsens the response to treatment of pancreatic cancer, in part by hampering surgery.

Although obesity is clearly associated with pancreatic cancer in patients from western countries, the relationship is for some reason less obvious in Japanese populations (Nitsche et al., 2011).

Because of the insidious onset of pancreatic tumours, there may be little impact upon a patient's quality of life until surgical treatment is required; still, less than a quarter of patients with pancreatic cancer survive long-term (Lee et al., 2012).

Michaud et al. (2001) tackled the issue of the relative impacts of obesity and physical activity (a detailed questionnaire assessment) on the risks of pancreatic cancer in a sample of 46,648 men and 117,041 women. A BMI >30 kg/m^2 was associated with a multivariate risk ratio of 1.72 (although unfortunately the calculation did not include physical activity as a covariate), and low levels of total physical activity (not adjusted for BMI) were associated with a rather similar increase of risk in those with a BMI >25 kg/m^2 (risk ratio 1.69). An illustration combined information on both tertiles of physical activity and BMI shows that the main adverse effect was seen with a combination of overweight or obesity and a low level of physical activity (Table 32).

Gallbladder disease. The rubric of gallbladder disease includes cholecystitis, gallstones and cancerous lesions of the gallbladder. Infections of the gallbladder have a strong linkage with obesity, and indeed as a young medical student, I was taught to suspect the presence of gall bladder disease in a woman who was fair, fat and forty, and presented with abdominal pain.

Table 32: Effects of BMI and physical activity tertile on the risk of pancreatic cancer. Relative risk ratios approximated from a figure of Michaud et al. (2001).

Physical activity tertile	BMI <25 kg/m^2	BMI 25.0-29.9 kg/m^2	BMI > 30 kg/m^2
High	1.0	1.02	1.10
Medium	1.05	1.25	0.90
Low	0.95	1.75	2.00

Cholecystitis and gallstones. Statistics point to a 28-45% prevalence of cholecystitis in middle-aged individuals who are morbidly obese, 3-4 times the risk seen in the general population, although surprisingly obesity no longer appears to increase risk in those aged > 50 years (Amarai and Thompson, 1985). Detailed data have accumulated mainly in small samples of patients undergoing surgical treatment.

The usually accepted explanation of pathogenesis is that the obese individual has a more cholesterol-saturated bile than a person of normal body mass (Mabee et al., 1976), whether due to a greater synthesis of cholesterol or a decreased synthesis of bile acids. Madura et al. (1979) related the presence of gallstones and the lithogenic index (the actual molar concentration of cholesterol relative to the maximum that can be held in solution, taking account of concentrations of bile salts and phospholipids) to body mass, expressed a percentage of the actuarial ideal. In 97 patients who were undergoing jejuno-ileal by-pass, there was an adverse trend in both factors when the most obese individuals in the sample (>267% of ideal body mass) were compared to those of normal body mass; gallstones were seen in 56% vs. 36%, and the lithogenic index was 1.66 vs.1.29. But unfortunately, given a limited sample size, neither of these differences were statistically significant. Nakeeb et al. (2002) found that a BMI > 30 kg/m^2 was a significant risk factor for symptomatic gallstone disease (a relative risk of 3.7 in a multivariate analysis that did not include physical activity). Other contributing factors included the female sex, age and a positive family history. A meta-analysis of four studies (Guh et al., 2009) found risk ratios of 1.20 for overweight and 1.43 for obesity in men, with corresponding figures of 1.27 and 1.78 in women. A further large-scale 8.8-year follow-up of male health professionals produced conclusive data for male patients (Tsai et al., 2004); the risk of developing gallstones in a cohort of 29,847 individuals who were initially free of biliary tract disease was 2.49 times greater in those with a BMI > 28.5 kg/m^2 than in those with a BMI < 22.2 kg/m^2. After adjusting for BMI and other known risk factors including an estimate of habitual physical activity (METs/week), the multivariate risk in those with a height-adjusted waist circumference > 103 cm relative to individuals with circumferences < 86 cm was 2.29. Likewise, those with a waist-hip ratio > 0.99 had a multivariate risk of 1.78 relative to those with a ratio <0.89. It thus seems that abdominal obesity has an adverse effect upon the risk of biliary disease, independently of any effects from BMI.

Dittrick et al. (2005) compared individuals who were morbidly obese and had undergone bariatric surgery (BMI >50 kg/m^2) with a group of potential liver transplant donors who were not obese. The morbidly obese fared worse than the controls in terms of both cholelithiasis (incidence 25% vs. 5%) and cholecystitis (50% vs. 17%). Moreover, the increase of

risk appeared to be proportional to the extent of obesity.

In a study of 58,400 Swedish twin pairs, a comparison of discharge diagnoses and deaths within pairs showed that the odds ratio for a report of symptomatic gallstones was 1.86 if one of the pair was overweight and 3.38 if one of the pair was obese (Katsika et al., 2007).

Cholecystitis can have a substantial adverse impact upon a person's quality of life (Table 33), with low scores seen for many domains of the SF-36 survey (Shi et al., 2008). There are dramatic gains 3 months post-surgery (Table 33), although one study of older patients found that the ultimate quality of life was rather similar for those treated surgically or conservatively (Vetrhus et al., 2005).

As with many of the conditions already discussed, there is growing evidence that a sedentary lifestyle also contributes to the development of gallstones (Sachdeva et al., 2011). Moreover, at least one analysis suggested that a 34% reduction of risk associated with the performance of 30 minutes of endurance exercise, 5 times per week, was achieved independently of the resulting control of obesity (Leitzmann, et al., 1998).

As discussed below, in the event that gallbladder surgery is required, it is much more difficult to perform in an obese patient than in an individual of normal body mass. One study estimated that 25% of hospital days associated with the treatment of gallbladder disease were attributable to obesity (Liu et al., 2008). Obese individuals were more likely to be admitted to hospital for treatment, and following admission they spent more days in hospital than their peers of normal body mass (44 vs. 16.5 days).

Cancer. Gallbladder cancer is relatively rare, but it was associated with obesity in an analysis of 8 studies (Randi et al., 2006); typically, the risk was doubled for those with a BMI between 30 and 35 kg/m^2.

Chronic renal disease. The issue of obesity and the risk of renal cancer has been discussed above. The potential role of obesity in causing a progression of chronic renal disease and micro-albuminuria has historically had limited recognition, but a number of recent epidemiological studies have shown that an association of overweight and obesity with chronic renal disease that is independent of other variables such as diabetes and hypertension. The analysis of Kitahara et al. (2014) focused upon nephritis, the nephrotic syndrome and nephrosis (International Classification of Diseases items No-No7, N17-N19, and N25-N27, and obesity increased the mortality per 100,000 for these conditions in women (20.7 vs. 2.7) but not

Table 33: SF-36 estimates of the quality of life in patients immediately prior to and 3 months after the surgical treatment of cholecystitis. Based on the data of Shi et al. (2008).

SF-36 Domain	Before surgery	3 months after cholecystectomy
Physical function	72.1	88.8
Role physical	51.3	81.6
Bodily pain	53.2	79.9
General health	56.7	60.5
Vitality	55.7	65.7
Social function	72.1	88.4
Emotional function	51.9	83.1
Mental health	59.0	68.7

in men (25.9 vs. 29.3).

Pathogenesis. Although hypertension, hyperinsulinaemia/insulin resistance and diabetes mellitus commonly play intermediate roles in the relationship between obesity and end-stage renal disease (Ferrannini and DeFronzo, 1989), disease progression can also occur more directly in response to the humoral secretions from fat deposits. Hyperinsulinaemia may stimulate smooth muscle proliferation in the media of the renal arterioles (Stout, Bierman, and Ross, 1975). It also sensitizes cells in the walls of the renal arterioles to the contraction-stimulating effects of angiotensin II (Kreisberg, 1982). Obesity thus becomes linked to focal and segmental glomerulo-sclerosis (Praga, 2002), with cytokines such as leptin, adiponectin, angiotensin II, TNF-alpha and IL-6 making significant contributions to renal vascular injury (Wolf, Chen, and Han, 2002). There may be hyper filtration, increases in intra-glomerular and renal venous pressures, and cytoxic effects from increased circulating levels of free fatty acids. End-consequences include nephrolithiasis, renal cancer and/or end-stage renal disease (Adelman, 2002; Kovesdy et al., 2017).

Epidemiology. Iseki et al. (2004) followed a sample of >100,000 men and women in Okinawa, Japan for 17 years. They observed an association between obesity and end-stage renal disease in male subjects that persisted after statistical allowance for the effects of age, hypertension and proteinuria (an odds ratio of 1.27 in a multiple logistic analysis). Moreover, there was some adverse effect even at relatively low BMI values (Table 34). Interestingly, there was no such effect in the female population (odds ratio 0.95). One possible explanation of the sex difference could be that women are generally less vulnerable to end-stage renal disease than their male counterparts. On the other hand, the study of Kitahara et al. (2014), which dealt with mortality rather than prevalence data, showed an adverse effect in men, but not in women.

A number of other studies have all demonstrated adverse effects of obesity upon the risk of developing chronic renal disease. An 18.5-year follow-up of 2585 initially healthy participants in the Framingham study (Fox et al., 2004) examined risk factors for the onset of renal disease (as defined by a glomerular filtration in the lowest fifth of the population distribution). A multivariate analysis allowing for age, sex, baseline glomerular filtration, smoking and diabetes found a statistically significant odds ratio of 1.23 per SD unit of BMI (4.2 kg/m^2); however, habitual physical activity was not included among their co-variates.

Data on 32,000 patients from the Kaiser Permanente Health Maintenance Organization likewise showed an adverse effect of a high BMI on the prevalence of

Table 34: Adjusted risk ratio* for developing end-stage renal disease over a 17-year follow-up. Based on the data of Iseki et al. (2004).

	BMI < 21 kg/m^2	BMI 21.0-23.1 kg/m^2	BMI 23.2-25.4 kg/m^2	BMI >25.5 kg/m^2
Men	1.0	1.79	1.95	2.39
Women	1.0	1.25[+]	0.88	0.96

[+] Not statistically significant

* Data adjusted for age, systolic blood pressure and proteinuria.

renal disease (Hsu et al., 2006). After allowing for other major risk factors including age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria at urinalysis, haematuria, and serum creatinine level (but not physical activity), the risk of end-stage renal disease increased progressively relative to individuals in the lowest BMI category (18.5-24.9 kg/m^2); hazard ratios were 1.27 for those who were overweight (BMI of 25.0-29.9 kg/m^2), 3.57 for those with stage 1 obesity (30.0-34.9 kg/m^2), 6.12 for stage 2 obesity (BMI 35.0-39.9 kg/m^2) and 7.07 for the most obese (BMI > 40 kg/m^2). Expansion of the study to a follow-up of 25 years on a sample of 177,570 Californian adults increased estimates of hazard ratios to 1.65 for the overweight, with values of 3.11 for Class I, and 4.39 for Class II-III obesity. The other main risk factors considered in this analysis were proteinuria and excess weight, but again there was no mention of possible effects from habitual physical activity (Hsu, et al., 2009).

Ejerblad et al. (2006) evaluated a sample of Swedes, detecting renal failure in terms of serum creatinine levels > 3.4 mg/L. They found that individuals with a BMI > 25 kg/m^2 at each of ages 20, 40 and 60 years had a 3-fold increase in the risk of developing chronic renal disease. The odds ratio for those with a BMI > 35 kg/m^2 was 2.2 for individuals without diabetes, 2.8 for those without hypertension, and 17.7 for those who had both stage 2 obesity and diabetes. Again, physical activity was not included among potential co-variates.

Lew et al. (2017) followed 52,777 Singapore Chinese for an average of 15.5 years. During this time, there were 827 incident cases of end-stage renal disease, and a clear relationship was seen between the development of renal problems and BMI (hazard ratios of 0.54, 1.00, 1.40, and 2.13 for respective BMI ranges of <18.5, 18.5-23.0, 23.0-27.5, and >27.5 kg/m^2). However, this dose-related trend was seen only among those with no history of diabetes, hypertension, coronary heart disease, or stroke.

Finally, Speckman et al. (2006) examined more than 25,000 patients who were receiving dialysis. After adjusting data for age, race, sex, primary cause of end-stage renal disease, history of diabetes, history of hypertension, and estimated glomerular filtration rate, the odds ratio for end-stage disease was 1.17 in those who were overweight, 1.25 for those who were obese, and 1.40 for those who were morbidly obese.

Quality of life. The quality of life is impaired from an early point in the course of chronic renal disease (Abdel-Kader et al., 2009; Pagels et al., 2012), with similar findings for chronic and end-stage disease; there is an emphasis upon low values for the physical components of the SF-36 scale, physical impairment being particularly marked in older individuals and those requiring dialysis (Crutz et al., 2011). Reduced haemoglobin levels were one correlate of low quality of life score (Crutz et al., 2011). Moreover, as with many chronic disorders, acceptance of the limitations imposed by chronic renal disease was an important determinant of quality of life (Poppe et al., 2013).

Interaction with physical activity. The physical activity level is typically low in chronic renal disease, but much of the sedentary lifestyle is a consequence rather than a cause of the condition (West et al., 2017). Nevertheless, an analysis of data from the National Health and

Examination Survey found that renal function was better in individuals with greater light and total physical activity (Hawkins et al., 2011), and the encouragement of greater physical activity can also help to redress some of the burden of chronic inflammatory activity associated with chronic renal disease (Dungey et al, 2013).

Respiratory problems

The analysis of Kitahara et al. (2014) centred its analysis of respiratory problems upon the diagnoses of influenza and pneumonia (International Classification of Diseases items J10-J18. There was a negative effect of obesity upon the mortality per 100,000 from these conditions in men (24.9 vs. 14.9), but not in women (11.6 vs. 10.1). A full analysis of respiratory issues also requires some consideration of asthma, which is rarely fatal, but has a substantial effect upon a person's quality of life.

Influenza. Perhaps because it causes a general, systemic chronic inflammation, obesity leads to an increased susceptibility to the influenza virus. This was first noted during the 2009 H1N1 epidemic, where associations were found between both the likelihood of hospitalization (odds ratio 1.6) and the risk of death (odds ratio 3.1)(Morgan et al., 2010). Even after successful vaccination, obese adults have double the risk of developing influenza (Green and Beck, 2017). The duration of infectiousness is also greater. A study of 1783 people in Managua, Nicaragua, found that following infection, obese adults continued to shed influenza type A virus for 42% longer, about 1.5 days, than people of normal body mass (Rubin, 2018).

The immediate symptoms of influenza are sufficiently short-lived to have no major impact upon healthy life years. However, a study of 24,656 adults in Hong Kong suggested that the regular practice of low to moderate intensity exercise was associated with a 4-6% decrease in the death rate from influenza (Wong et al., 2008).

Pneumonia. Overweight and obese individuals are at an increased risk of pneumonia (odds ratio 1.33)(Nie et al., 2014). A Danish study noted that the risk of hospitalization for pneumonia was also greater in obese males (hazard ratios of 1.4 for moderate, and 2.0 for severe obesity), although risks were not increased in obese females (Kornum et al., 2010). However, an obesity paradox has also been described (Nie et al., 2014), whereby obesity does not have any great impact upon the mortality from pneumonia; indeed, in one sample of U.S. patients the odds ratio for death from pneumonia was 0.86 in those who were obese (King et al., 2015).

Habitual physical activity was not associated with the risk of pneumonia in one sample of male smokers who had been administered vitamin E and beta-carotene (Hemilä et al., 2006), and a slight trend to protection from vigorous physical activity was also statistically insignificant in women (Neuman et al., 2010). On the other hand, in the institutionalized elderly, the risk of pneumonia was 60% higher in those with a low Barthel score who were finding difficulty in performing the activities of daily living (Wójkowska-Macha et al., 2013).

Asthma. The accumulation of body fat is associated with an increased risk of asthma, with a significant impact upon quality-adjusted life expectancy for the

affected individual and (in the case of children) for their families (Hossny et al., 2017). The first studies to advance this idea, both for adults (Camargo et al., 1999) and for children (Castro-Rodriguez et al., 2001), appeared some 20 years ago. As in a number of other co-morbidities, fat-induced chronic inflammation was suggested as a possible causal factor.

The NHANES studies of American adults (Ford and Mannino, 2005) found that the age-adjusted prevalence of asthma was greater in those who were obese (21-33%) than in those who were not (15-23%). Likewise, studies in boys <14 years have linked asthma to obesity (Figueora-Munoz et al., 2001; Mannino and Ferdinands, 2006). A retrospective study of 143 non-smokers attending an asthma clinic also found that obesity contributed to the severity of asthma (Akerman et al., 2004). A meta-analysis of 4 BMI-based studies set asthma risk ratios in men at 1.20 for those who were overweight and 1.43 for those who were obese, with corresponding figures of 1.25 and 1.78 for women (Guh et al., 2009).

Ferreira et al. (2010) estimated the mean utility value at 0.86 for patients with asthma. This reflected mainly limitations in physical functioning, and utility values were lower in those who were employed in physically demanding occupations. Advanced age, a lower level of education and poor control of the asthma also lower the quality of life (Gonzalez-Barcella et al., 2012).

Once again, the relative contributions of obesity and a sedentary lifestyle to the risks of asthma remain to be clarified (ten Hacken, 2009). An animal study compared sedentary rats to those having access to an exercise wheel, and found the former were more vulnerable to ozone-induced asthmatic attacks (Gordon et al., 2017). Likewise, human data found that watching television was associated with an odds ratio of 1.76 for current wheezing, and 1.60 for exercise-induced wheezing (Asani and Jakupi, 2008), a view confirmed by a review of 11 available studies (Konstantanki et al., 2014). This could indicate that physical activity protects against asthma, but it is also possible that the risk of asthma may have encouraged the adoption of sedentary leisure pursuits.

Osteoarthritis and chronic back pain

Osteoarthritis and chronic back pain do not affect mortality, but they are two major sources of reduced quality-adjusted life expectancy, and obesity bears some of the responsibility for the causation of these problems. Plainly, the greater body mass of the obese person, often accompanied by an age- and inactivity-related weakening of the skeletal musculature, places an increased strain on degenerating joints, whether in the knees or the spine, with an increased risk of chronic back pain and symptoms of osteoarthritis in other major joints.

Chronic back pain. One early report suggested that the linkage between obesity and chronic back pain was controversial, and as yet undetermined (Mirtz and Greene, 2005), in part because of the vagueness of the diagnosis. There is also a problem of causation, in that chronic back pain is likely to limit movement, and thus predispose to obesity.

A 7-year prospective study of 34,754 workers looked cross-sectionally at the likelihood of premature retirement due to chronic back pain (Hagen et al., 2002). These investigators found a risk ratio of 1.59 in workers who were overweight, and of 2.81 in those who were obese. In a multivariate analysis that included

measures of involvement in physically demanding work (but not habitual physical activity), poor general health and smoking, a BMI in the upper quartile of the sample distribution carried an odds ratio of 1.6. Chou et al. (2016) noted further that chronic low back pain was significantly associated with both BMI and waist-hip ratio, but the reported severity of pain was markedly augmented by mood disorders.

A meta-analysis, based upon 24 cross-sectional and nine cohort studies, mostly with allowance for physical workload and psychosocial stressors, confirmed consistent associations with obesity; odds ratios relative to those of normal weight were 1.33 for those reporting back pain during the past 12 months and 1.50 for those seeking treatment of lower back pain (Shiri et al., 2010). A further recent meta-analysis was based on 10 cohort studies (a total of 29,748 subjects); it, also, showed fat accumulation as a consistent risk factor for low back pain, with respective odds ratios of 1.15 and 1.36 for overweight men and women, and ratios of 1.36 and 1.24 for those who were obese (Zhang et al.,2018).

On average, low back pain reduces the quality of life by 35%, but there is a wide range of variation about this mean value (Schaller et al., 2015); depression scores are closely correlated with a substantial decrease in the quality of life.

In terms of interactions with physical activity, cross-sectional data suggest that complaints of low back pain are more frequent in those undertaking heavy occupational exercise and intensive leisure exercise activity, but that regular moderate exercise is associated with a lesser prevalence of low back pain than that seen in inactive individuals (Schaller et al., 2015).

Osteoarthritis. Obesity is associated with an increased risk of osteoarthritis, probably through a combination of mechanical and metabolic pathways (Eaton, 2004). In terms of the impact of osteoarthritis upon physical function, the knee and hip joints are particular sources of disability, with obesity being one of the most important risk factors in terms of both causation and disease progression (Grazio and Balen, 2009).

***Epidemiology*.** A comparison between 525 patients aged >45 years undergoing knee surgery and 525 controls showed that the risk of osteoarthritis requiring surgery relative to those with a BMI of 24.0-24.9 kg/m^2 (1.0) increased steeply to 13.6 in those with a BMI >36 kg/m^2; the authors of this report estimated that if only a quarter of obese individuals reduced their body mass by 5 kg, 24% of knee operations could be avoided (Coggon, Reading, and Croft, 2001). Other reports have shown an association between obesity and similarly large risk ratios (Table 35).

A follow-up of knee pathologies in 715 middle-aged women found that over a 4-ear interval, some 12.6% of the sample developed radiographic joint-space narrowing (a rate of about 3.1% per year), but no clear risk factors for this change were identified. Some 13.3% of the group also developed osteophytes (a rate of about 3.3% per year). After adjusting data for the use of hormone replacement therapy, hysterectomy, smoking, knee pain and social class, those in the top tertile of BMI had a significantly greater incidence of osteophytic changes relative to those in the lowest tertile of BMI (Hart et al., 1999), with an odds ratio of 2.38. The extent of habitual physical activity was apparently assessed from simple questions related to walking,

Table 35: Studies examining the risk of osteoarthritis of the knee joint in obese individuals, relative to those with a normal body mass.

Author	Sample	Obesity criterion	Odds or Risk ratio
Coggon et al. (2001)	525 knee surgery patients >45 yr	BMI >36 kg/m^2	13.6
Felson, et al. (1997)	Framingham residents, initially aged 70.5 yr	5 kg/m^2 greater BMI	1.6 over 10-yr follow-up
Grotle et al. (2008)	1675 Norwegians aged 24-76 yr	BMI >30 kg/m^2	2.8 over 10- yr follow-up (adjusted for occupational and leisure activity)
Hart et al. (1999)	715 middle-aged women	Top vs. bottom tertile of BMI	2.38
Holliday et al. (2011)	1042 knee osteo-arthritis patients, 1121 controls	BMI >30 kg/m^2	7.48 vs. case controls
Lohmander et al. (2009)	27,960 Swedes	First vs. 4th quartile on obesity markers	8.1 over 11 yr follow-up (data adjusted for physical activity)
Reijman et al. (2007)	3585 people > 55yr	BMI >27 kg/m^2	3.3 over 66 yr follow-up
Toivanen et al. (2010)	829 Finnish patients initially free of osteoarthritis	BMI >30 kg/m^2	7.0 at 22-yr follow-up

occupational activity and sport participation, and on this basis, the development of osteophytes appeared to be unrelated to habitual activity levels.

In a 10-year follow-up of Framingham residents who at an age of 70.5 years were initially free of knee osteoarthritis, a multivariate analysis that included physical activity and many other variables found a 1.6 increase in the risk of developing radiographic osteoarthritis for each 5-unit increase of BMI (Felson et al., 1997). However, in this report, risks of osteoarthritis were also least in that quartile who reported the lowest level of habitual physical activity on the Framingham Index (a score based on the number of reported hours per day spent at each of several levels of activity).

The study of Lohmander et al. (2009) is particularly comprehensive. It followed 11,026 men and 16,934 women from the general population over an 11-year period. Risk ratios were compared for the first and fourth quartiles of obesity markers. After adjusting for age, smoking and habitual physical activity as measured by the Framingham index, risk ratios for the knee joint were BMI 8.1, waist circumference 6.7, body weight 6.5, percent body fat 3.6 and weight-hip ratio 2.2. The corresponding figures for osteoarthritis of the hip were BMI 2.6, body weight 3.0, waist circumference 2.5, waist-hip ratio 1.3, and percentage body fat 1.5.

In accord with this demonstration of the much smaller impact of osteoarthritis upon the hips, relative to the knees, Reijman et al. (2007) commented that obesity seemed to affect the knee but not the hip joint. In a sample of 3585 people aged > 55 years who were followed for an average of 6.6 years, after adjusting data for age, sex and follow-up time, radiographs showed a 3.3-fold greater risk of incident knee osteoarthritis and a 3.2 fold greater risk of disease

progression (as shown by a decrease in joint space) in those with a BMI > 27 kg/m^2 relative to individuals with a normal body mass. Misalignment of the knee joint may have been a contributing factor, since in this sample obesity had little impact on the incidence of osteoarthritis of the hips (Reijman et al., 2007).

A prospective study of 5784 individuals aged >50 years also found that obesity had a substantial influence on the risk of developing self-reported disabling knee pain (Jinks et al., 2006). A 3-year follow-up of study participants found a 1.66-fold increase in the risk of developing severe knee pain in those who were obese relative to those with a normal BMI, after adjusting data for age, sex, anxiety, depression, previous knee injury, baseline pain, more general perceptions of pain and laterality. The authors of this report underlined that 30% of severe pain would likely have been avoided if patients had reduced their weight by one category (obese to overweight, or overweight to normal weight).

The adverse effect of obesity on the risk of developing osteoarthritis has been confirmed in many other investigations. Tukker et al. (2009) made a cross-sectional evaluation of Dutch adults aged >25 years; in this sample, even moderate overweight was associated with self-reported osteoarthritis (an unadjusted odds ratio of 1.7), chronic pain (odds ratio 1.6), and problems in mobility (odds ratio 1.7). For those who had become obese, the corresponding odds ratios were 2.8, 2.5 and 3.0. Moreover, Sutbeyaz et al. (2007) noted that osteoarthritis led to a significant decrease in aerobic power as assessed by peak oxygen intake (0.99 vs. 1.58 L/min) and in the distance that obese patients could walk in 6 minutes ($p < 0.001$), with this inactivity presumably predisposing to the development of obesity.

Joint replacement treatment. Three studies looked at the risks of joint replacement surgery (Guh et al., 2009). In men, the average risk ratios were 2.76 for the overweight and 4.20 for the obese, and in women the corresponding numbers were 1.80 and 1.96.

***Quality of life*.** Sutbeyaz et al. (2007) compared the quality of life between 28 obese individuals who had osteoarthritis and 28 obese controls of similar gage (average 44 years). Limitations of aerobic power were significantly correlated with several SF-36 components, including bodily pain, general health, and physical role limitations. Another study of 93 patients with knee osteoarthritis, also using the SF-36 questionnaire (Kawano et al., 2015), found a very low quality of life (Table 36), with the domains of functional capacity, functional limitation and pain being particularly affected. Moreover, the impact was greatest in those with a low level of educational attainment, perhaps because the nature of their employment required physical activity.

Desmeules et al. (2009) noted that in their sample, scores for both the physical and mental domains of the SF-36 survey had dropped below the 25th percentile of values for control groups, with respective average scores of 28 and 43. Mahir et al. (2016) also measured the SF-36 scores, among other measures of quality of life finding average values of 41 (Physical) and 44 (Mental). And in New Zealand, the lifetime effect of osteoarthritis was estimated at a loss of 3.4 quality-adjusted life years (Abbot et al., 2017). Similarly large decreases in the quality of life have been seen in those with osteoarthritis of

Table 36: Quality of life on the SF-36 survey as observed in a Brasilian sample of 93 patients with osteoarthritis. Based on the data of Kawano, Araűjo, and Castro (2015).

SF-36 domain	Score
Physical function	37.1
Role physical	25.1
Bodily pain	32.9
General health	54.6
Vitality	48.7
Social function	50.1
Emotional function	38.6
Mental health	60.1

the hip (Boutron et al., 2008).

Interaction with physical activity. Sports with a high risk of physical injury predispose to osteoarthritis as a person ages. Prolonged vigorous low impact exercise does not seem to increase the risk of osteoarthritis, but high levels of impact and torsional loading do increase risks significantly. A number of studies looking at the risks have co-varied for obesity, but it is important to keep in mind that pain from osteoarthritis can restrict physical activity and thus lead to a secondary development of obesity (Lane, 1996).

Increased risks of surgery

Anyone who has worked in an operating room can attest to the difficulty of performing abdominal surgery on those who are grossly obese. There is a likelihood that the operation time, will be longer, and that there will be a greater blood loss. The mechanical problems of the surgeon are often compounded by the poor initial cardio-respiratory and metabolic function of those who are obese, together with problems of haemostasis (Pasulka et al., 1986). But paradoxically, comparisons of patients who are above the ideal weight with those below this standard suggest that the immediate risks of operation are not increased for the heavier individuals (Tjeertes et al., 2015). The obese certainly encounter significant problems in the post-operative period, with delayed wound healing, and incisions that frequently become infected and/or burst open, but nevertheless a greater than desirable body weight has surprisingly little impact upon the long-term survival from general surgery (Tjeertes et al., 2015).

This paradox immediately highlights the problem of using BMI as a surrogate of body fat content or composition. Those who undergo surgery with a low BMI are commonly cigarette smokers and patients whose bodies have been weakened by cancerous lesions. There remains a need for an assessment of the risks of surgery based on other measures of body fat such as skin-fold data, making comparisons between the obese and those of normal body mass, rather than with patients who have undergone cancerous wasting.

One study of infections following spinal surgery found no impact of obesity when this was defined by BMI, but when skin-fold thickness was used as the criterion of fat accumulation, the risk of post-operative infection was 5.0% in the non-obese, compared with 15.2% in those who were obese (Waisbren et al., 2010). Another report noted that relative to patients with a normal body mass, obese patients had a higher prevalence of myocardial infarction, peripheral nerve injury, wound infection and urinary tract infection. Moreover, morbidly obese patients had double the operative mortality rate of other patients, with a higher prevalence of tracheal reintubation and of cardiac arrest (Bamgbade et al., 2007).

Accidents, mental illnesses and suicides

The substantial adverse influence of obesity upon the incidence of accidents, mental illness and suicides, associated increases in mortality and deterioration in the quality of life, have already been discussed in the previous part of this review (Shephard, 2018c).

Discussion and Conclusions

Obesity is associated with an increased incidence of and mortality from a wide range of chronic conditions. Much of the existing data looks at overall death rates from obesity and the impact of various co-morbidities in terms of risk ratios. However, there is a need to present such information as losses in years of calendar life and quality-adjusted expectancy, not only for the individual client but also for those formulating population policy, with such calculations taking due account of the possible impact of habitual physical activity and changing patterns of treatment upon such estimates of risk. Although the shortening of lifespan seems relatively small for those who are a few kg overweight, in severe obesity losses of life expectancy can apparently amount to 5 years or more, with further substantial losses in terms of quality-adjusted life years.

Despite a substantial volume of epidemiologic research, the precise impact of obesity upon mortality and quality of life remains unclear, since the majority of studies of this topic completed to date have not co-varied data for the possible influence of inter-individual differences in habitual physical inactivity. Nevertheless, it is well established that a sedentary lifestyle can reduce life expectancy by several years (Paffenbarger et al., 1990), equally in thin and heavier individuals (Barlow et al., 1995), and since obese individuals are typically less active than those who are thinner, it remains to be clarified how large a part a lack of adequate physical activity has played in the shortening of their lifespan. The apparently smaller impact of obesity upon mortality in older individuals certainly mimics the effects associated with a lower level of habitual physical activity in older people (Paffenbarger et al., 1990), but a few of the studies cited, such as Moore et al. (2008), have pointed to seemingly independent negative effects of obesity and an inactive lifestyle upon mortality. There is also a need to clarify possible influence from reverse causality, as often chronic disease reduces habitual physical activity, and this predisposes to obesity.

Obesity apparently has a substantial impact upon prognosis in various pre-existing chronic conditions. The largest adverse effect is seen in type 2 diabetes mellitus, where gross obesity is associated with a 6.3-fold increase of mortality in men, and a 3.5-fold increase in women. Longitudinal observations further suggest that the risk is increased if a person with diabetes gains weight, and that it is decreased if he or she reduces body mass. Studies seeking to disentangle the respective influences of obesity and physical activity upon the decrease of life expectancy associated with the metabolic syndrome are in especial need of further evaluation, since the method presently used to assess the independent influence of aerobic fitness (treadmill running time) is itself heavily dependent upon the individual's body mass.

To date, analyses of additional obesity-related losses from a deterioration in health-related quality of life have sometimes shown what might be judged as a relatively small effect. However, it is important to underline that a 25%

decrease in the quality of life, if sustained over 40 years of survival, equates to a cumulative loss of 10 years. Moreover, many assessments have been made in middle age, and the impact of co-morbidities upon the quality of life is likely to increase in the final years of life.

There remains a need for fundamental research on the mechanisms underlying the toxic effects of fat accumulation on various body tissues, including the heart, and to determine how far hormonal changes speed the growth of cancers. Overall, obesity probably increases premature mortality by 70-80%, with additional losses of disease-free years, although there is a need for statistics showing the cumulative losses associated with varying degrees of obesity. How important is this from a health policy perspective? Statistics Canada estimated that in 2009/2011, the average remaining life expectancy of Canadians at the age of 65 years was 18.8 years for men, and 21.7 years for women. Despite medical advances, there are still age-related deteriorations of the senses and the mind in advanced age, and many people may not consider the extension of their lifespan beyond the age of 80 or 90 years a strong argument for correcting obesity. However, a poor quality of life during the final 20-30 years of survival should be a greater cause of concern, offering a strong argument for maintaining an acceptable body mass and for correcting any current accumulation of body fat through an increase of physical activity and a restriction of food intake.

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Author's Qualifications

The author's qualifications are as follows: Roy J. Shephard, C.M., Ph.D., M.B.B.S., M.D. [Lond.], D.P.E., LL.D., D.Sc., FACSM, FCSEP, FFIMS.

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